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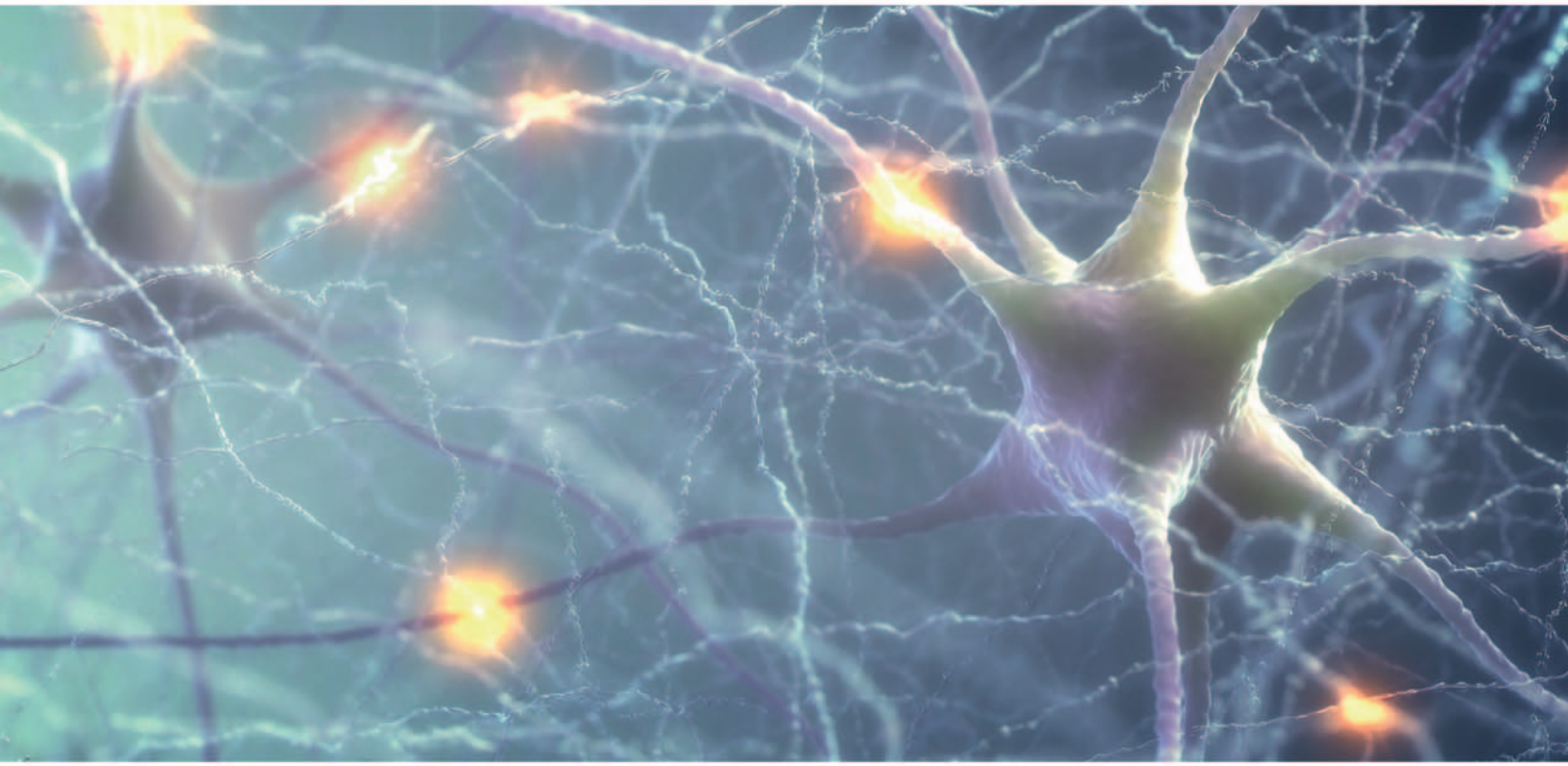
Handbook of *In Vivo* Neural Plasticity Techniques

A Systems Neuroscience Approach to the Neural Basis of Memory and Cognition



Edited by Denise Manahan-Vaughan

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HANDBOOK OF *IN VIVO* NEURAL PLASTICITY TECHNIQUES

A SYSTEMS NEUROSCIENCE APPROACH TO THE NEURAL BASIS OF MEMORY AND COGNITION

Edited by

DENISE MANAHAN-VAUGHAN

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CHAPTER

21

Repetitive Sensory Stimulation—A Canonical Approach to Control the Induction of Human Learning at a Behavioral and Neural Level

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1. INTRODUCTION

1.1 Research Perspective

Heritable features, evolving during evolutional time spans, are of ultimate advantage for survival and are, without exception, structurally fixed. To cope successfully with the ongoing changes of environmental conditions occurring during the lifespan of an individual, additional mechanisms are required that allow rapid and effective adaptations that are not specified by genetic constraints.

Given these obvious needs for plastic adaptations, it appears only natural that brain plasticity of various forms represents a general and ubiquitous feature present in all sensory and motor modalities (Dinse and Böhmer, 2002). In this context, it appears surprising that the notion of adult neuroplasticity only became established in the late 1980s of the last century. Before that, the neuroscience community regarded adult brains as being nonplastic (Kaas et al., 1983). However, it should be emphasized that despite the presence of plastic capacities, systems must possess sufficient generic stability to warrant secure processing. Conceivably, there is a trade-off between modifiability and stability.

Perception, behavior, and cognition are not constant, but rather change throughout a lifespan. Development and aging are major determinants, as are alterations following brain injuries. Other factors that instigate plastic changes arise from constraints during everyday life. Examples comprise particularities of occupation including lifestyle and prolonged episodes of intense sensory stimulation, such as those occurring in blind Braille readers, or musicians. While it takes several tens of thousands of hours of intense practice to develop musical skills typically observed in professional musicians (Ericsson et al., 1993; Macnamara et al., 2014), even short periods of several minutes of training and practicing can induce learning processes leading to significant gains in performance (Poggio et al., 1992).

Independent of the duration and type of training, it is generally agreed that modification of synaptic efficacy is the primary neural substrate for learning (Teyler and Discenna, 1984; Morris, 1990). While it is well documented that synaptic plasticity mechanisms either facilitate or suppress transmission at synapses to alter communication between nerve cells, their relevance to behavioral experience remains debated. Long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission comprise persistent forms of activity-dependent changes in synaptic strength (Nicoll and Malenka, 1995). Both forms are related to the acquisition of long-term spatial and/or associative memory (Kemp and Manahan-Vaughan, 2007). Typically, high-frequency stimulation is used to induce LTP in brain slices and in behaving rodents, whereas LTD can be reliably evoked by low-frequency stimulation (Bliss and Collingridge, 1993, Malenka and Bear, 2004, Lynch, 2004; Kemp and Manahan-Vaughan, 2007).

In addition to LTP/LTD mechanisms, spike-timing-dependent plasticity (STDP) mechanisms have attracted

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much interest over the last few years. STDP assumes that there are narrow and cell type–specific temporal windows for synaptic modification induced by the correlated spiking of presynaptic and postsynaptic neurons, depending on the temporal order of spiking (Bi and Poo, 2001; Dan and Poo, 2004). LTP effects are induced when presynaptic spikes are emitted before the postsynaptic neuron starts to spike, and LTD effects are induced when presynaptic spikes are emitted after the postsynaptic neuron starts to spike. In contrast to LTP and LTD, the relationship of STDP to behavioral leaning is currently unclear.

1.2 How to Study Synaptic Plasticity in Humans

The lack of adequate input stimuli for the induction of LTP and LTD in humans has hindered direct evaluation of the impact of such protocols on human behavior. Which role is played by LTP or LTD in human learning? Are these relevant processes at all to understand what happens during everyday learning? Synaptic plasticity studies use temporally specific stimulation protocols to induce long-lasting changes in synaptic transmission, but the implications of this requirement for temporally specific protocols in everyday learning outside the laboratory remain unclear. For training- and practice-based learning to occur, sensory inputs are modified in their frequency, temporal pattern, and the number of stimuli and their duration, form, size, and intensity (Sasaki et al., 2010; Sagi, 2011). However, it is difficult to exactly quantify the numerous changes in input parameters that occur during training. Therefore, linking the principles of synaptic learning that induce plasticity at the cellular level to the principles at the systems level is far from straightforward. Similarly, although the significance of STDP mechanisms in network formation and in coding of temporal sequence patterns has been recognized, the implementation of STDP principles in human learning experiments is difficult because of the problem of assigning a temporal order to sensory inputs (but see study McMahon and Leopold, 2012, for successful implementation).

1.3 The Rationale Behind Repetitive Sensory Stimulation

An interesting alternative is offered by a reverse approach that takes advantage of the broad knowledge of brain plasticity to design specific sensory stimulation protocols that allow changes in brain organization and, thus, perception and behavior. The idea is to translate protocols that induce plasticity at a cellular level into sensory stimulation protocols. This approach has the unique advantage of offering complete control of the timing and spatiotemporal allocation of the stimulation (Fig. 21.1). Moreover, this approach is not only an ideal tool for applying known protocols to humans to assess whether such protocols can affect human perception and behavior but also a means to systematically determine the appropriate timing for the induction of perceptual and cortical changes in humans, which can result in temporal stimulation protocols that have so far not investigated in synaptic plasticity research (Dinse et al., 2011; Dinse and Tegenthoff, 2015). Another advantage is that the experimental designs applied in humans can be transferred one-to-one to animal models, which allows further investigation of pharmacological and molecular mechanisms underlying repetitive sensory stimulation effects.

From a practical perspective, the approach of repetitive sensory stimulation bears a number of advantages: it is cost-effective, and it does not require expensive technologies and apparatus. It is a safe approach with no adverse effects known so far, and it is easy to use. In principle, it can be used to target every desired location within sensory cortical representations with high precision in terms of localization. Moreover, the size of the target region depends on the layout of stimulation, thus allowing highly localized induction of plastic changes.

The approach we report here can be regarded as extremely robust. So far, we have studied several hundred cohorts of participants covering the lifespan of 10–90 years totaling several thousand participants.

1.4 Terminology—Relation to Other Groups

The concept of sensory stimulation protocols to induce learning has attracted substantial interest and is currently being investigated in many laboratories. However, different laboratories use different terms to refer processes that are essentially comparable, such as "peripheral nerve stimulation" (Sawaki et al., 2006), "somatosensory stimulation" (Conforto et al., 2002; Wu et al., 2006), "unattended-based learning" (Dinse et al., 2005), "repetitive sensory stimulation," or "high-frequency stimulation" (Ragert et al., 2008). The idea of "coactivation" emphasizes the relevance of Hebbian learning, where synchronous neural activity is instrumental to drive plastic changes (Hebb, 1949). Other laboratories use the framework of "tetanic" stimulation, or use the term "stimulus-selective response plasticity" (Teyler et al., 2005; Clapp et al., 2012). The term "exposure-based learning" has been introduced to indicate that mere exposure is sufficient to drive perceptual changes (Gutnisky et al., 2009). As a suggestion for unification, the term "training-independent sensory learning" was introduced to characterize all types of

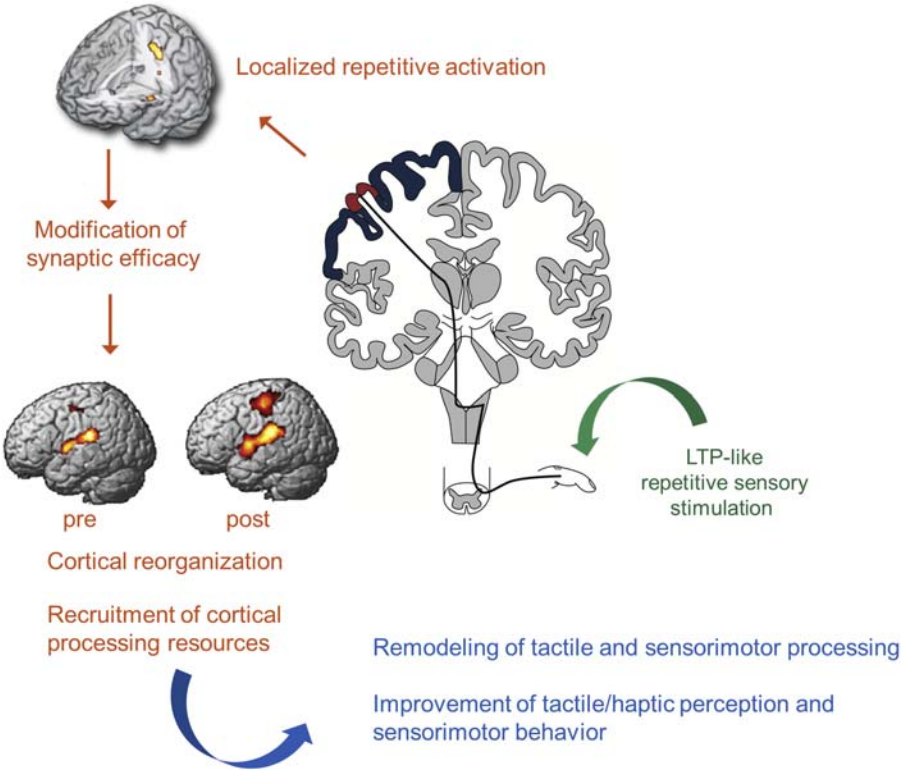

FIGURE 21.1 Schematic illustration of the assumed chain of changes evoked by repetitive stimulation. Sensory stimulation of a finger induces a cascade of functional alterations within the sensory system being targeted, leading to the induction of plastic processes, which in turn result in behavioral/perceptual changes. *LTP*, long-term potentiation.

learning induced by synaptic plasticity protocols in human participants with the aim of changing perception and behavior (Dinse and Tegenthoff, 2015). The frequently used term "passive stimulation", or "passive learning" is meant to indicate that a subject is exposed to repetitive sensory stimulation in a task-free situation without actively attending to the stimulation. We use the term "repetitive sensory stimulation" throughout this chapter.

1.5 Strategy and Target of Stimulation—Relationship to Other Techniques

Accordingly, the underlying principle and the aimed target of repetitive sensory stimulation differs from that of functional electrical stimulation (FES), or therapeutic electrical stimulation such as neuromuscular electrical stimulation (NMES) or transcutaneous stimulation (TENS) (Wilson et al., 2016; de Kroon et al., 2002). These forms of electrical stimulation are currently used in rehabilitation with mixed results. FES is applied to induce contraction of muscles to support motor action. On the other hand, therapeutic electrical stimulation methods are applied to improve performance after the termination of stimulation, such as NMES, EMG-triggered electrical stimulation (EMG-ES), and TENS. Although TENS was introduced for pain treatment, effects observed after NMES and EMG-ES are assumed to be related to repetitive muscle contractions. For each method, a wide range of stimulation parameters are in use, and the underlying mechanisms mediating beneficial effects remain largely to be clarified.

Central to using repetitive sensory stimulation is its ability to drive and facilitate neuroplasticity processes, a property shared by central stimulation approaches such as intracortical microstimulation, transcranial direct current stimulation, and transcranial magnetic stimulation (Elsner et al., 2016; Hao et al., 2013). While intracortical microstimulation is a highly effective tool to induce locally plastic changes (Nudo et al., 1990; Recanzone et al., 1992a,b), for central stimulation techniques the aspects of safety, cost efficiency, and localization of stimulation need to be taken into consideration (Pascual-Leone et al., 1993).

1.6 Rationales for Studying Somatosensory Systems

In the following sections, the use of repetitive sensory stimulation will be discussed as an example for the somatosensory system, although its use is not limited to

this sensory modality, but can also be used for studies targeting the visual, auditory, and nociceptive domains (see Section 3.9). The reasons for selecting the somatosensory system are manifold: the somatosensory cortex was the first in which adult neuroplasticity was demonstrated (Merzenich et al., 1984). Subsequently, the somatosensory system was intensively investigated to find limits and rules underlying these adult plastic changes. It is indeed the case that plastic changes can be induced comparatively easily in the somatosensory system. (For a discussion of modality-specific constraints see Dinse and Böhmer, 2002). From a practical point of view, although to date, repetitive sensory stimulation has been successfully applied in all three sensory modalities; the largest body of data, and thus the richest expertise for inducing plastic changes, has been accumulated for the somatosensory system.

2. METHODOLOGICAL CONSIDERATIONS

This section summarizes the current state of the art, which is almost certainly far from optimal, and calls for further exploration of the potential of this approach in terms of details of timing of stimulation protocols. Moreover, one of the many aspects that await further investigation is the role of temporal spacing of stimulation such as duration, breaks, or repetitions to further optimize outcome of plastic changes.

2.1 Implementation

2.1.1 Temporal Properties of Repetitive Sensory Stimulation—Pulse Statistics

Passive stimulation has the unique property of offering full control with regard to the timing and spatiotemporal spacing of stimulation. Thus, passive stimulation is an ideal tool for the systematic exploration of the requirements for the induction of perceptual and cortical changes through synaptic plasticity protocols. In the past, many different patterns of stimulation were successfully applied. (For an overview, see Parianen Lesemann et al., 2015.) The effects induced by these different patterns largely follow the logic behind the LTP−LTD models that are well established in synaptic plasticity research.

2.1.1.1 Long-term Potentiation− and Long-term Depression−Like Stimulation Protocols

In humans, the investigation of direct cellular analogues of LTP and LTD is limited to patient groups in whom single-cell recordings can be made (i.e., Beck et al., 2000). Therefore, indirect approaches are needed to explore the relevance and efficacy of these *in vitro* protocols in driving behavioral changes in humans *in vivo*. To this aim, we translated LTP and LTD protocols into tactile high- and low-frequency stimulation pattern preserving the aspects of timing. The terms "LTP- and LTD-like" is meant to emphasize the analogy to cellular protocols. In most experiments, tactile high-frequency stimulation (tHFS) consisted of intermittent pulse trains of 20 single pulses of 20 Hz with an intertrain interval of several seconds. In contrast, low-frequency stimulation (tLFS) is most applied at continuous 1 Hz trains (Ragert et al., 2008). Other studies have used variable frequencies between 18 and 24 Hz with interpulse intervals varied randomly between 3 and 10 s to avoid habituation effects (Reuter et al., 2014). Some studies used 20-Hz bursts with ramp/fall times of 0.5 s (cf. Heba et al., 2016). For extensive review see Parianen Lesemann et al. (2015).

2.1.1.2 Coactivation Protocols

A "tactile coactivation" protocol was introduced to study the relevance of Hebbian learning in humans: In this case, synchronous neural activity, necessary to drive plastic changes, is evoked by tactile coactivation of the skin (Godde et al., 1996, Godde et al., 2000; Dinse et al. 2003; Pleger et al., 2001, 2003). The basic idea is to coactivate a large number of receptive fields in a Hebbian manner, to strengthen their mutual interconnectivity. For this approach, coactivation stimuli were drawn from a Poisson process with interstimulus intervals ranging between 100 and 3000 ms in pseudorandomized order. Although the average stimulation frequency is 1 Hz, the frequency dominating is around 10 Hz.

The coactivation approach not only offers the advantage of studying synchronicity effects but more generally permits scrutiny of the role of stimulation timing for the induction of plasticity responses. For example, coactivation protocols have been used to compare effects of synchronous and asynchronous stimulation (Pilz et al., 2004; Kalisch et al., 2007). A particular feature of repetitive stimulation is that dependent on stimulation protocol, bidirectional plastic changes can be evoked. Besides the described protocols here, the approach offers the unique opportunity to explore new pattern of stimulation that might be even more effective in driving plastic changes.

2.1.2 Application of Repetitive Sensory Stimulation—Somatosensory System

The question how to apply repetitive sensory stimulation depends on the sensory modality (see also Section 3.9). As a rule of thumb, almost every kind of approach is feasible. So far, most studies in the somatosensory system focused on studies exploring plastic changes of the cortical finger/hand representations, which can be

induced following stimulation of these body parts. Apparently, the approach can be used for studies targeting any desired body part. Certain body parts such as fingers, face, and feet are overrepresented in the homuncular structure of somatosensory cortex. The resulting large cortical territories clearly facilitate experiments addressing reorganizational map changes, which are much more difficult to perform when investigating body parts with cortical underrepresentations such as the arm or the torso. Our own recent studies demonstrated by contrast that the exploration of plastic changes of perceptual abilities is possible on the forearm as well (Muret and Dinse, 2018).

To apply repetitive sensory stimulation, a number of approaches have been used in the past. In principle, it is possible to use either cutaneous or electrical stimulation. Depending on the research question, the repetitive stimulation protocol can be applied to a single finger or all fingers of a hand.

2.1.2.1 Cutaneous Stimulation

Mini Speaker An easy and cost-effective way of application is the use of a small mechanical actuator that can be taped to the fingertip or any other desired location on the body. A small solenoid from a mini speaker with a diameter of 8 mm is a popular choice. The solenoid allows simultaneous stimulation of the skin portions of the finger under the solenoid leading to coactivation of all receptive fields within this area; for an estimate of receptive field sizes of the human index finger see Vega-Bermudez and Johnson, 1999. According to these data, receptive fields within 8 mm of the tip of the index finger overlap partially or are nonoverlapping (Fig. 21.2).

Double Pins This approach uses two independent movable pins, which allow testing assumptions concerning Hebbian plasticity, as well as the role of synchronicity for inducing plasticity. We have used a custom-made small device (diameter 20 × 10 mm) consisting of two small stimulators made from tiny relay modules (Fig. 21.2). The device can be taped to the finger. Stimulation is transmitted via two needles (diameter 0.5 mm) with a distance of 6 mm to the skin (Höffken et al., 2007).

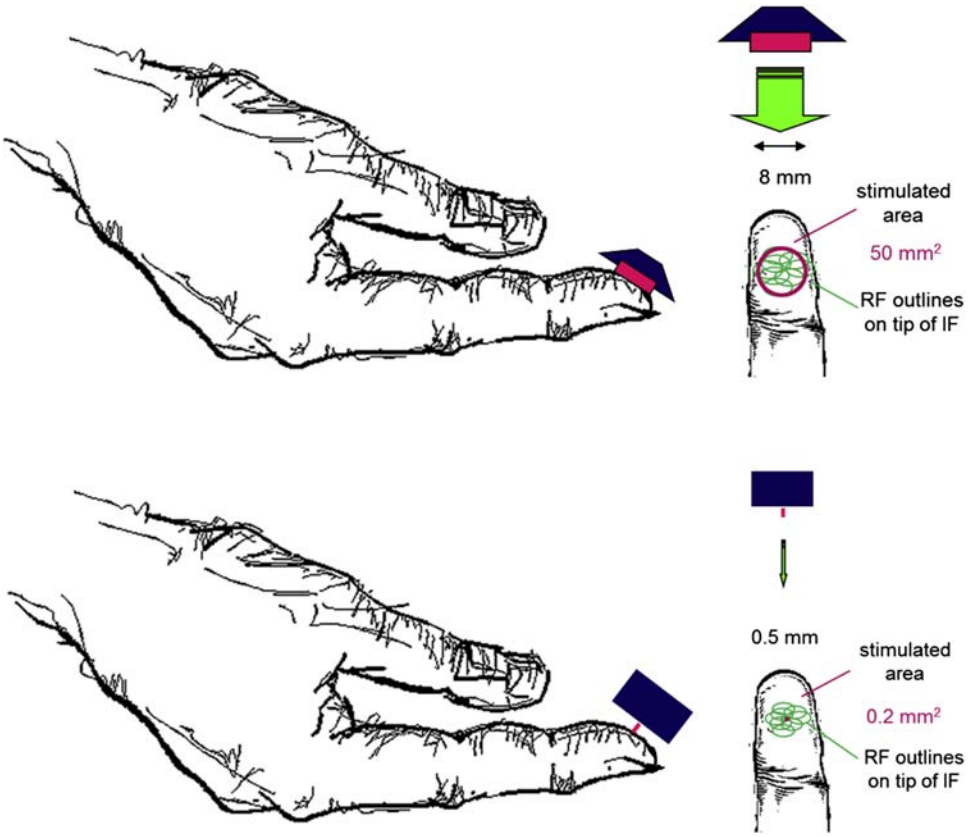

FIGURE 21.2 Application of coactivation: (Top) A small mechanical actuator with a diameter of 8 mm is mounted on the tip of the right index finger to coactivate the receptive fields (RFs) representing the skin portion under the solenoid (50 mm^2). (Bottom) Control protocol. Application of a so-called single-site stimulation: A small device consisting of only one tiny actuator (tip diameter 0.5 mm) is mounted on the tip of the right IF (index finger) to stimulate a single "point" (0.2 mm^2).

Braille Modules Braille modules consist of two rows of tiny piezo-driven pins. Stimulation is possible by controlling either a single pin or several pins, thus allowing patterned tactile stimulation (Reuter et al., 2014).

2.1.2.2 Electrical Stimulation

To apply electrical repetitive stimulation, electrical pulses can be transmitted via adhesive surface electrodes fixed to the first and third finger segment (cathode proximal), either to a single finger or to all fingers of a hand (Fig. 21.3). For stimulation of all fingers, the use of adhesive electrodes is possible but is very time consuming. Instead, for this application, the use of stimulation gloves with inbuilt electrode pairs on each finger is advantageous (Fig. 21.3).

In this case, to account for the innervation of the fingers, where stimulation thresholds vary between the median and ulnaris nerve innervated fingers, the stimulation for the predominantly median nerve−innervated fingers d1−d3 (the thumb, index, and middle finger) and the predominantly ulnar nerve−innervated fingers d4 and d5 (ring and little finger) can be separately controlled and delivered.

It should be noted that gloves with this type of electrode configuration enable clearly defined stimulation of the fingertips. It is also possible to record somatosensory evoked potentials (SEPs) or to measure BOLD (blood oxygenation level−dependent) signals in the scanner while applying repetitive sensory stimulation. Fig. 21.4 shows an example of BOLD activity as well as SEPs obtained during stimulation using a custom-made stimulation glove (Fig. 21.4). Another advantage of using gloves for stimulation of all fingers of a hand, is the resulting larger cortical activation and associated plastic changes, which can be useful dependent on experimental question (cf. Heba et al., 2016, 2017; Kattenstroth et al., 2018). Most importantly, single-finger contact gloves use a profoundly different strategy than the so-called mesh gloves or whole hand stimulation approaches, where the entire hand is diffusely stimulated.

2.1.3 Control Conditions

To provide a control for the Hebbian nature of the coactivation and to rule out that unspecific factors are unlikely to contribute to the coactivation effects, it can be useful to apply a so-called single-site stimulation. For that purpose, the same stimulator can be used as described above for "double pin" stimulation. However, for a control condition, only a single probe (diameter 0.5 mm) is used. In that way, a single "point" (0.2 mm^2) is stimulated instead of coactivating a large area of 50 mm^2 (Fig. 21.2).

FIGURE 21.3 Electrical repetitive finger stimulation. Left: Adhesive surface electrodes fixed to the first and third finger segment transmit electrical pulses (cathode proximal). This configuration can be used to stimulate a single finger or all fingers of a hand. To account for innervation of the fingers, the stimulation for the predominantly median nerve-innervated fingers d1−d3 (the thumb, index, and middle finger) and the predominantly ulnar nerve-innervated fingers d4 and d5 (ring and little finger) were separately controlled and delivered. Right: Stimulation glove with inbuilt electrodes contacting the first and third finger segments of each finger to transmit electrical pulses (cathode proximal). Same two channel stimulation strategy as shown left.

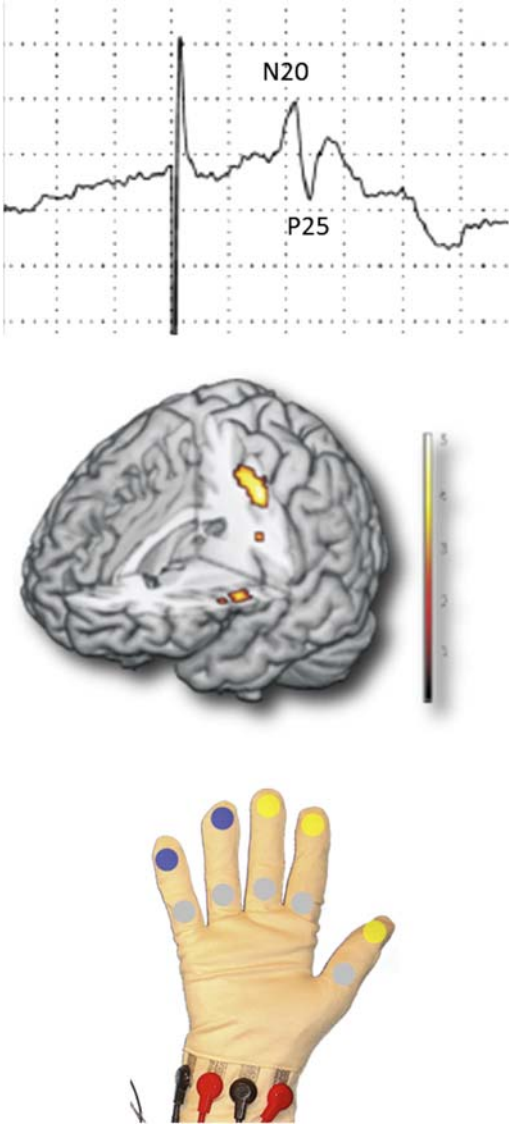

FIGURE 21.4 Cortical activation recorded following stimulation using the stimulation glove. Top: Somatosensory evoked potential (SEP) negativity upward, N20 and P25 components indicated. Grid gives 10 ms on the abscissa and 1.5 μV on the ordinate. Middle: BOLD (blood oxygenation level−dependent) responses in primary and secondary somatosensory cortices of a single subject as recorded in a 3 Tesla scanner indicating MR (magnetic resonance) compatibility. Bottom: Schematic illustration of the stimulation glove with contact points; *yellow* indicates median nerve-innervated fingers, *blue* indicates ulnar nerve-innervated fingers, and *gray* gives indifferent electrodes.

2.1.4 *Intensity and Duration of Stimulation*

Cutaneous stimulation does not need high amplitudes. Laser vibrometer measurements revealed that amplitudes of 10−20 microns are sufficient to drive robustly plastic changes (Dinse et al., 2006). In contrast for electrical stimulation, which target not the mechanoreceptors but the afferent nerves, the highest tolerable stimulation intensities result in largest effects (Schlieper and Dinse, 2011). Duration of cutaneous pulses can vary between 10 and 1000 ms; in case of electrical pulses, typically 200 microns are used.

2.1.5 *Generation and Storage of Pulse Sequences*

A pulse can be generated online during the experiment by means of standard stimulus generators. When using cutaneous stimulation, appropriate amplifiers are needed to drive the actuators. In case of electrical stimulation, stimulus isolators provide the connection to the electrodes. To allow unrestrained mobility of the subjects during repetitive stimulation, pulses can be digitally recorded and then played back.

2.1.6 *Other Sensory Modalities*

A couple of studies used repetitive stimulation to investigate plastic changes of visual perception (Pegado et al., 2016; Marzoll et al., 2018). Most studies used monitors to display the type of visual stimulus needed, which all require fixed position of the subjects during stimulation. The development of novel approaches such as Oculus Thrift or HTC Vive allows more comfortable experimental settings with subjects being able to move around during stimulation.

2.2 Assessment of Changes

2.2.1 *What to Assess—Behavior*

The sense of touch is a so-called "near sense," which requires direct contact between skin and stimulus. In contrast, vision as a far sense can be studied by presenting stimuli on a monitor, where stimuli can be easily varied. For analyzing the sense of touch, a battery of physical devices is needed, which are then brought into contact with the skin. Therefore, investigation of the sense of touch is much more difficult and time-consuming.

The sense of touch is not a uniform entity, but comprises quite diverse features. From an operational point of view, investigation of the sense of touch requires breaking down performance and functions related to touch into measurable variables. It appears conceivable to refer to the idea of a hierarchy of tasks and tasks complexities, which differ in the involvement of proprioception and motor functions and in the amount of cognitive demand. Accordingly, the underlying neural substrates differentially involve, in a graded way, contribution from the periphery and from various cortical areas, including so-called primary, input-receiving areas as well as higher order, associative, and often multimodal areas.

A central aspect of passive stimulation is that sensorimotor improvement is not induced through training of a particular task but through modification of synaptic efficacy in neural networks. Therefore, it had been

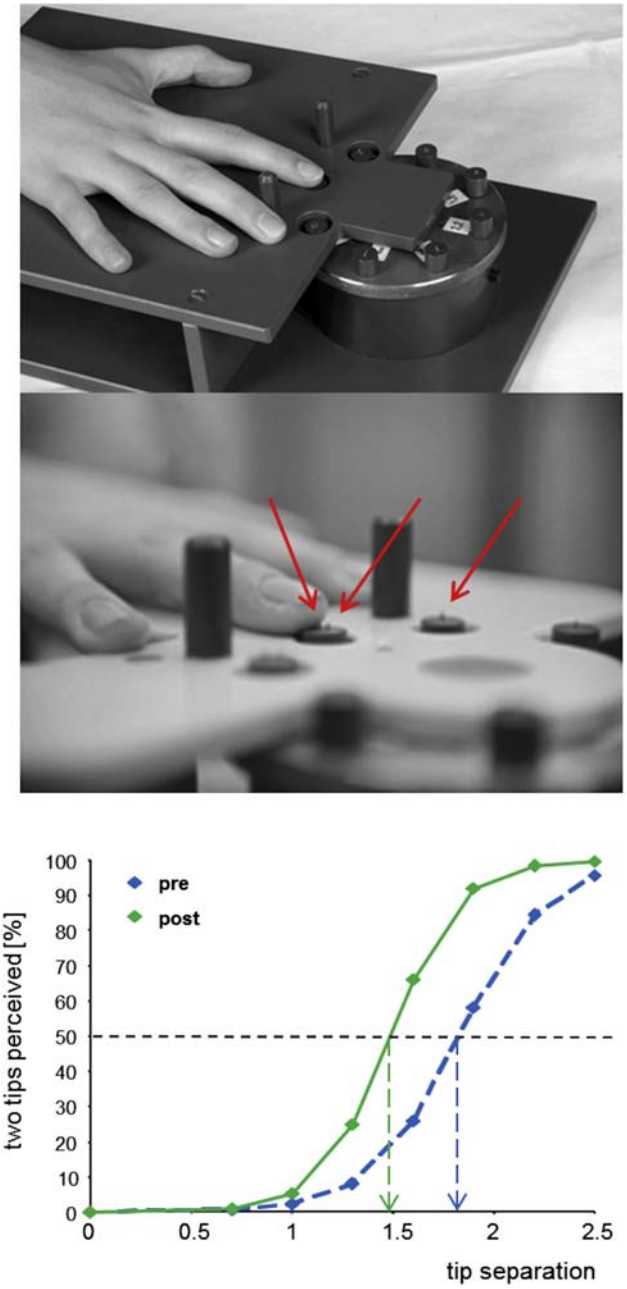

FIGURE 21.5 Two-point discrimination test. Top: Testing device. The subject's forearm, hand, and fingers are fixed on a plate that, for each presentation, can be moved downward to a rotatable disk with the test finger being placed over a small hole within the plate. The downward movement is stopped at a fixed position above the pins through which the test finger touches the pins at the same indentations for each presentation. Middle: Seven pairs of pins (for older adults separated by 1.0, 1.4, 1.8, 2.2, 2.6, 3.2, and 4 mm; for young adults by 0.7, 1.0, 1.3, 1.6, 1.9, 2.2, and 2.5 mm) and one single pin (*arrows*) were circularly mounted on a rotatable disk. Each single pin had a diameter of 200 microns. Participants are required to promptly report whether they felt "one" or "two" probes. Emphasis is laid on answering "two" only when clearly perceiving two distinct points. When perceiving a bar, a bigger point, or any unclear shape, participants were instructed to answer "one." This procedure corresponds to an improved version of the classical two-point discrimination task. In this modified version, the threshold does not correspond to the distinction between one tip versus two tips but to the decision when two tips are sufficiently separated to be perceived as two. Bottom: To this aim, the entire psychometric curves are computed and then used to determine the distance at which participants reported the sensation of two clearly separated tips (as compared with two tips less distant, perceived as one tip). Ordinate: Percent two tips perceived, abscissa tip separation. *Diamonds* give measured responses; *curves* give binary logistic regression. Shown are measurements before (*blue*) and after (*green*) repetitive stimulation resulting in lowered thresholds (50% correct).

hypothesized that passive stimulation remodels the entire way of neural processing related to tactile, haptic, and sensorimotor information processing in a task-independent way. This hypothesis predicts that passive stimulation does not affect a particular subfeature of tactile processing. Instead, passive stimulation can be expected to affect almost all spatial and temporal features involving tactile, haptic, and sensorimotor processing.

A simple and reliable marker of the quality of the sense of touch is tactile acuity, which, equivalent to visual acuity, characterizes the spatial discrimination abilities. There are many ways to measure and quantify fine spatial discrimination such as two-point discrimination, letter recognition, or gap detection. While in the past we and other groups have routinely used a modified two-point discrimination task (Godde et al., 2000, Dinse et al., 2003a,b; Pleger et al., 2001, 2003), another often used test for tactile acuity is the grating orientation task(GOT) (Van Boven and Johnson, 1994). While there is an ongoing controversy about what constitutes the most appropriate acuity test, for us, the guiding arguments for selecting two-point discrimination as a simple and basic measure of tactile perception is to have a test that is easy to implement and easy to use (Fig. 21.5). As we are interested in somatosensory cortical reorganization, the test should address properties of tactile information processing with little confound from cognitive contributions such as imagery, mental rotation, or cross-modal resources, which is the case for GOT (Zhang et al., 2005). In addition, the underlying mechanism should be interpretable in terms of cortical processing to allow computational modeling (Dinse et al., 2008; Wilimzig et al., 2012; Pleger et al., 2016; Philipp et al., 2018).

To obtain information about possible changes of basic tactile perceptual abilities beyond acuity, other tests such as measurement of fine-touch sensitivity with von Frey filaments (often called Semmes-Weinstein filaments) are used, which measures minimal touch threshold (Kumar et al., 1991). In another, so-called mislocalization test, fingers of the hand are stimulated near threshold, which evokes localization errors, i.e., a neighboring finger other than the stimulated one is incorrectly perceived as being stimulated (Schweizer et al., 2001).

A cognitively more demanding task is the ability to recognize objects by their haptic impression. We used

a set of different groups of unfamiliar cubic objects made from common LEGO™ bricks, which had to be explored by haptic perception only thus providing information about haptic object recognition abilities (Dinse et al., 2005, Kalisch et al., 2008, 2010). To assess dexterity and fine-motor performance of the hand and finger, the peg-board test is suggested as a standard and appropriate task (Kowalewski et al., 2012). To assess tactile reaction times, multiple-choice reaction time measurements can be performed (Wilimzig et al., 2012).

Performance of temporal processing can be reliably tested in a two-alternative, forced-choice frequency discrimination task as introduced in the 1970s by LaMotte and Mountcastle (1975). An alternative approach consists of evaluation of the minimum interval between two stimuli that are clearly perceived as being separated (Erro et al., 2016).

All of these described test options have so far been used in repetitive stimulation experiments. But clearly, the final choice depends on the nature and the question of any potential experiment.

2.2.2 *What to Assess—Neural Processing*

What has been described above for assessment of behavioral changes, the task-free nature of repetitive sensory stimulation makes no *a priori* assumption about possible neural changes. Yet, when investigating the somatosensory system, changes along the tactile pathways and the somatosensory cortex and beyond are to be expected.

Features analyzed so far include cortical activity by means of EEG (electroencephalography) or MEG (magnetoencephalography), as well as noninvasive measuring of BOLD signals by magnetic resonance imaging. Data have also been collected characterizing brain rhythms, functional connective, resting state changes, GABA (gamma-aminobutyric acid) concentrations by means of magnetic resonance spectroscopy, structural properties such as gray matter density, and event-related potentials.

While so far most studies used a pre–post design, where neural changes were recorded twice before and after repetitive sensory stimulation (Pleger et al., 2001, 2003, Dinse et al., 2003a,b; Höffken et al., 2007), recent studies showed that it is possible to record neural activity during application of repetitive sensory stimulation as well. For example, using a 64 channel EEG recording changes of somatosensory cortical α-power has been investigated (Freyer et al., 2013).

2.3 Ubiquitous Experimental Set-up

A typical experiment comprises—depending on the question—at least three components: First, before stimulation, baseline perceptual/sensorimotor performance needs to be assessed, as well as cortical activation parameters recorded (precondition). Then, the repetitive stimulation protocol is applied. Afterward, a second assessment serves to quantify the efficacy of the stimulation-induced learning processes (postcondition). Additional follow-up tests can be implemented to obtain information about time course, stability, and duration of stimulation-induced alterations (recovery).

While the overall design is simple, it allows accommodating almost any kind of participant groups, any kind of experimental questions including drug studies, additional interventions, and any kind of assessment of induced alterations.

2.4 Interindividual Variability

As detailed in section 3.6 "Predicting learning outcome," there is a huge variability of the effects of repetitive sensory stimulation. This variability is due to the many factors that impact upon learning processes (see Section 3.6). This is regularly observed in all kind of learning and plasticity experiments and is in no way specific to repetitive stimulation approaches. On the contrary, as repetitive stimulation controls many more factors than do training-based studies, the learning variability might be even lower. In Fig. 21.6 a representative example of variability within a randomly selected group of 80 participants is shown. While most participants show the average gain in tactile discrimination, many subjects exhibit deviating responses, either by showing unusual high learning or by showing little or no learning at all. When designing experiments, this variability can be expected and should be taken into account.

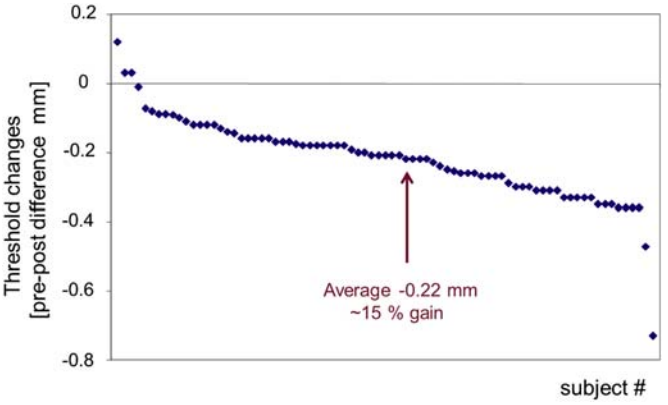

FIGURE 21.6 Variability of learning outcome following a long-term potentiation (LTP)–like repetitive sensory stimulation experiment. Each *dot* represents a single participant (total N = 80) ordered according to the stimulation-induced difference in two-point discrimination threshold pre–post (ordinate). Average improvement, corresponding to a lowering in threshold, is indicated together with percent gain. Note substantial individual scatter ranging from very strong improvement to even impairment.

2.5 Trouble Shooting

Generally, problems can arise from three independent factors: First, there can be problems with the behavioral/neural assessment, making it difficult to see effects. Second, specific characteristics of the participants can hinder the detection of effects. This can include inadequate sensory abilities to run the tests, problems in concentration, and willingness to cooperate, as well as neurological problems related to effective processing and general learning deficits. Third, there can be problems with the technical aspects of stimulation, such that stimulation is not correctly transmitted, not perceived, or otherwise corrupted.

2.5.1 Problems With Assessment

As in all psychophysical testing, subject instructions play a crucial role, as does subject compliance and cooperativity. Overly extensive assessments, particularly when testing strained skin and finger sensitivity, might interfere with stimulation results. In many experiments, a break of at least 15 min after termination of stimulation is often introduced; however, its role and significance remains to be further clarified. When assessments are used that induce a significant practice-related task improvement, these effects may conceal stimulation-induced effects, or piggyback on the stimulation-induced changes.

So far, time of the day of testing has not been found to be crucial, but this aspect might need further investigation.

2.5.2 Participants

A large number of factors have been identified that affect learning processes. These include genetic factors such as BDNF (brain-derived neurotrophic factor) polymorphisms that are present in about one third of the population. Other factors are morphological properties of individual brains such as gray matter thickness (Conde et al., 2012), GABA concentrations (Heba et al., 2016), or α-power (Freyer et al., 2013). Gender might play a role owing to hormonal cycles, and, indirectly related to gender, finger size (Peters et al., 2009). Of course, intense finger use, as is the case in musicians (Ragert et al., 2004), blind individuals (Wong et al., 2011), or fine mechanics (Reuter et al., 2012), alters baseline performance as well as plastic capacities (Ragert et al., 2004). Clearly, all these constraints need to be taken into consideration when designing experiments.

2.5.3 Stimulation

In case of cutaneous stimulation that targets mechanoreceptors, stimulation amplitude can be small. For example, stimulation amplitudes of 20 μm are sufficient (Godde et al., 2000; Dinse et al., 2006). On the other hand, in the case of electrical stimulation, which targets the peripheral nerves, a high stimulation current yields better results (Schlieper and Dinse, 2011). The duration of stimulation can be as short as 15 or 20 min when using LTP-/LTD-like protocols. When using irregular patterns as in case of coactivation, 3 h are needed, with 30 min being ineffective (Godde et al., 2000).

Generally, LTP-like protocols are more robust with less variability in outcome as compared with LTD-like protocols. Stability of effects is usually many hours, so even extended assessment is possible.

3. OVERVIEW OF AVAILABLE DATA ABOUT EFFECTS OF REPETITIVE SENSORY STIMULATION

3.1 Perceptual Effects

3.1.1 Stimulation-Induced Alteration of Tactile and Sensorimotor Behavior

The basic effects of repetitive sensory stimulation on tactile acuity (two-point discrimination) are illustrated in Fig. 21.7. In this experiment, the fingertip of the right index finger was stimulated with a coactivation protocol as described in Section 2.1.1.2, using brief taps of 10 ms duration, which were transmitted to the skin via a small movable membrane (mini loudspeaker). Before stimulation, all participants showed stable performance over repeated assessment sessions. After coactivation, subjects without exception improved their acuity as indicated by a lowering of thresholds by approximately 15%. Retesting after 24 h revealed restoration of initial baseline performance. These results were the first to show that it is possible to evoke improvement of the sense of touch in human subjects solely through a few hours of passive, but temporally patterned, stimulation (Godde et al., 1996, 2000).

To demonstrate the Hebbian nature of the coactivation protocol, the effects of coactivation were compared with those of a so-called "single-site stimulation," where only a small "pointlike" skin area was stimulated. Stimulating the finger at a single site did not induce changes in discrimination performance or brain activity (Pleger et al., 2003). This indicates a lack of brain reorganization and suggests that it is unlikely that other tasks beyond discrimination might have benefitted from single-site stimulation. These results imply that a Hebbian "coactivation" is crucial for the induction of plasticity effects and point to the requirement of spatial cooperative processes. Furthermore, the data emphasize that not all types of sensory stimulation can lead to perceptual changes and that there are "simple" forms of stimulation that remain ineffective in driving plasticity.

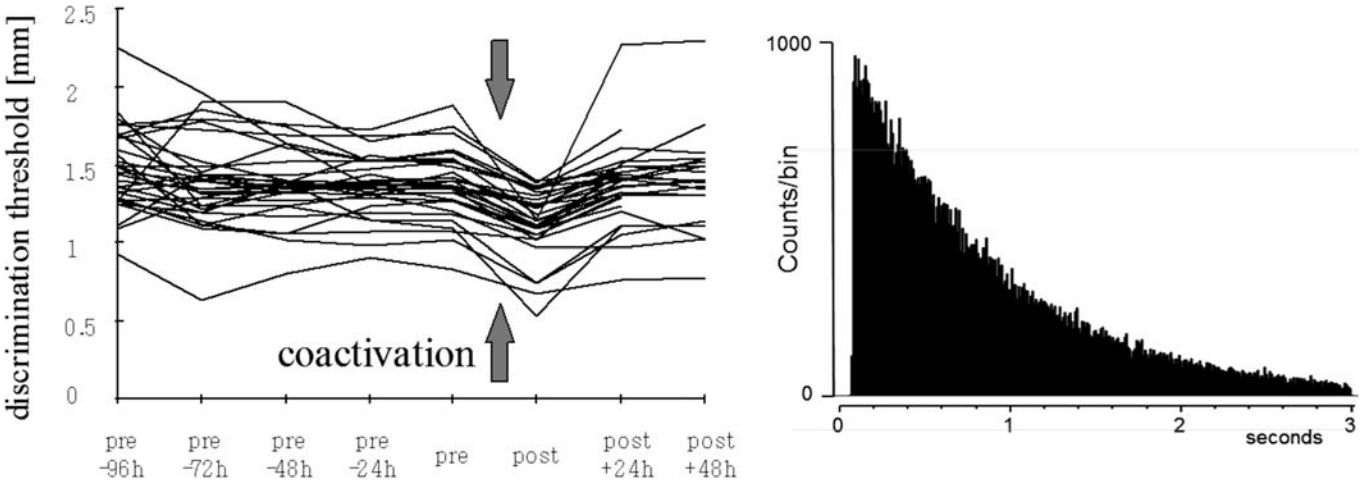

FIGURE 21.7 Left: Effects of coactivation, a form of repetitive stimulation, on tactile acuity (tactile two-point discrimination) of the index finger of the right hand in 35 subjects (each *line* is one subject). Thresholds were measured 5 days before and immediately after coactivation (*arrows*) and on two subsequent days. In all subjects, after coactivation thresholds were reduced, on average by approximately 15%, but returned to control values 1 day after termination of stimulation. Right: Stimuli used for coactivation were drawn from a Poisson process (ISIs truncated <100 ms and >3000 ms).

3.1.2 *Bidirectional Changes Are Synchrony Dependent*

Evidence that simultaneity plays, in fact, a crucial role for induction of plastic changes comes from experiments comparing the effects of synchronous versus asynchronous stimulation. At a cortical level, representations for synchronously coactivated fingers moved closer together whereas cortical representations for asynchronously coactivated fingers became segregated (Pilz et al., 2004). Behaviorally, synchronous stimulation improved acuity and increased mislocalization between fingers while asynchronous stimulation imposed the opposite effects (Pilz et al., 2004; van der Berg and Dinse, unpublished; Kalisch et al., 2007).

3.1.3 *Bidirectional Changes Are Frequency Dependent*

To explore the relevance and efficacy of the *in vitro* LTP/LTD protocols in driving perceptual changes in humans, they were translated into tactile high- and low-frequency stimulation patterns. As little as 20 min of high-frequency stimulation induced a lowering of tactile discrimination thresholds, whereas low-frequency stimulation resulted in an impaired discrimination performance (Ragert et al., 2008). These results indicate that brief stimulation protocols (<30 min) resembling those used in cellular LTP and LTD studies can induce bidirectional, frequency-dependent, relevant, and persistent alterations in tactile discrimination behavior of humans (Fig. 21.8).

3.1.4 *Temporal Processing*

Besides spatial aspects of tactile perception, temporal processing is also affected by repetitive sensory stimulation. Using a somatosensory temporal discrimination task, it was shown that in addition to improved spatial acuity, temporal discrimination (defined as the minimum interval between two stimuli that are clearly perceived as being separate) improves after 45 min of an LTP-like stimulation protocol (Erro et al., 2016). Using a standard frequency discrimination task, a 3 h coactivation protocol was reported to result in lower discrimination thresholds (Dash and Dinse, unpublished; Reuter et al., 2014).

3.2 Alteration of Cortical Processing

Important parameters, for the characterization of cortical processing and its changes, comprise the size and extent of cortical activation, which is often interpreted as reflecting cortical maps and map reorganization (Buonomano and Merzenich, 1998). It could be shown that after repetitive sensory stimulation, which leads to improved acuity, the sensorimotor cortical regions representing the stimulated finger were increased in size (Dinse et al., 2003a,b; Pleger et al., 2001, 2003; Hodzic et al., 2004) (Fig. 21.3). These findings were interpreted as a recruitment of processing resources to make processing more efficient. Under the assumption that changes of cortical maps representing the stimulated finger reflect changes in cortical processing causally related to the processing of tactile information, it was hypothesized that cortical alterations should correlate with the changes in individual performance. Linear correlation analysis revealed significant relations between the stimulation-induced cortical map changes and the parallel improvement in two-point discrimination ability (Fig. 21.9). Accordingly, low gain in spatial

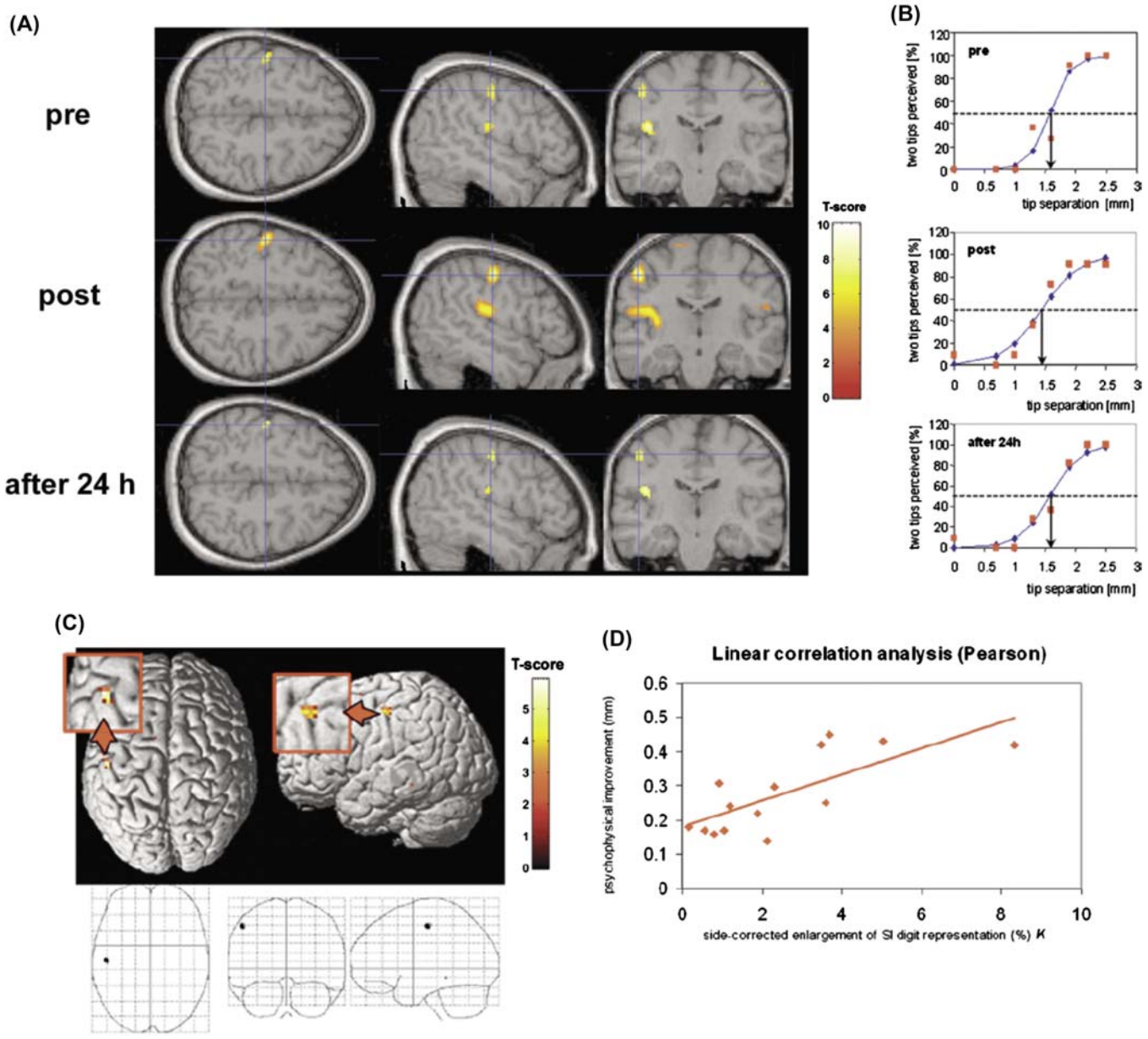

FIGURE 21.8 Effects of coactivation on tactile acuity and associated cortical reorganization. (A) BOLD signals detected pre, post, and 24 h after coactivation in the contralateral SI in the postcentral gyrus and in the contralateral SII in the parietal operculum above the Sylvian fissure. Activations are projected on an axial (left), sagittal (middle), and coronar (right) T1-weighted, normalized magnetic resonance imaging (MRI) slice. Comparing pre- with postcoactivation functional magnetic resonance imaging (fMRI) sessions revealed enlarged activation and increased BOLD signal intensity in SI and SII contralateral to the coactivated IF. These changes of BOLD signal characteristics recovered 24 h after coactivation was applied. (B) Psychometric functions illustrating the coactivation-induced improvement of discrimination threshold for the subject shown in (A). Correct responses in percent (*red squares*) are plotted as a function of separation distance together with the results of a logistic regression line (*blue with blue diamonds*). 50% levels of correct responses are shown as well as thresholds. Top, precondition before coactivation; middle, postcondition, immediately after coactivation; bottom, recovery after 24 h. After coactivation there is a distinct shift in the psychometric functions toward lower separation distances, which recovers to preconditions 24 h later. (C) Relationship between changes in BOLD signals and coactivation induced changes of two-point discrimination thresholds. Results revealed a significant correlation between perceptual and cortical changes within SI on the postcentral gyrus (see also magnified detail). In contrast, no activated clusters were found within SII. (D) Linear correlation analysis between perceptual and cortical changes in SI (Pearson) corroborated these findings. The corresponding number of activated voxels per cluster, K = ([rightpost − rightpre] − [leftpost − leftpre])/rightpre, was correlated with coactivation-induced changes in psychophysical thresholds ($r = 0.744$; $P = .002$).

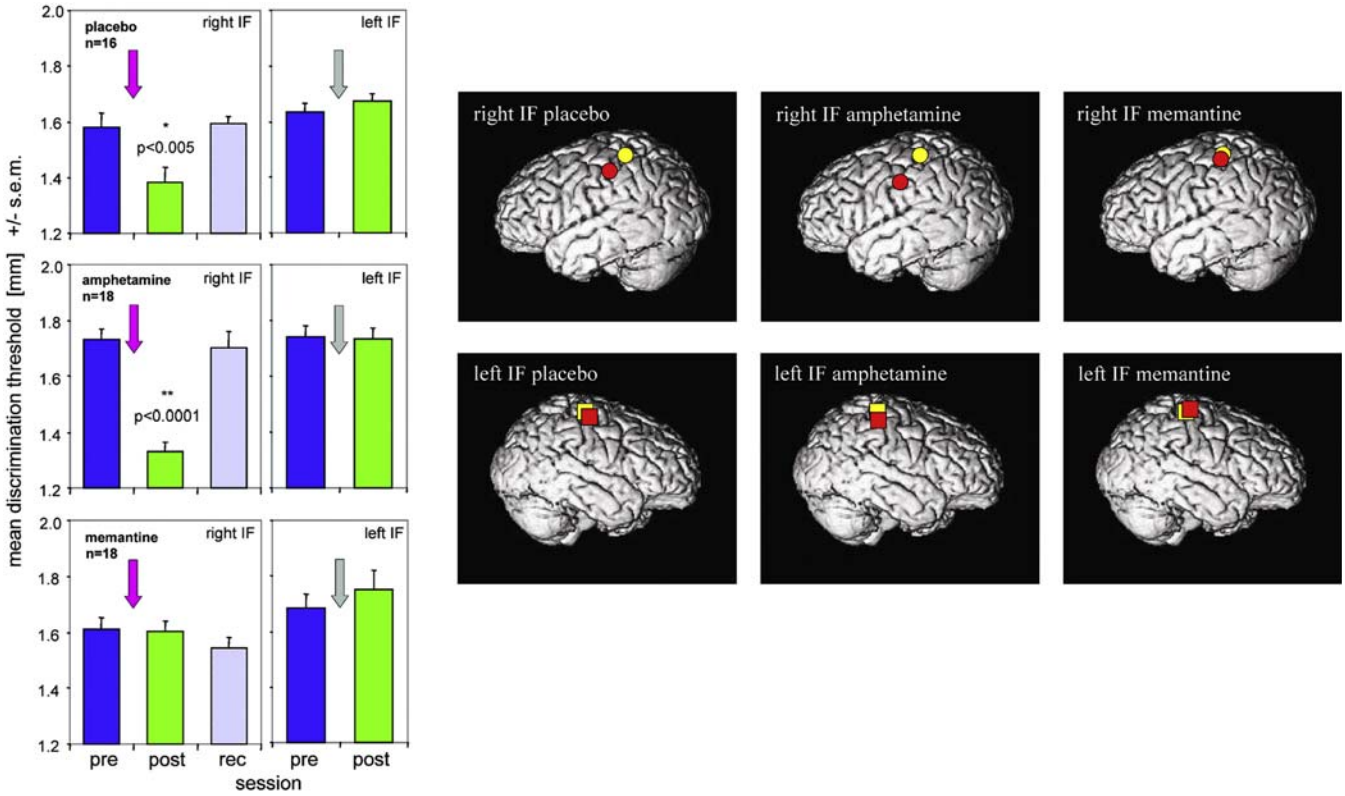

FIGURE 21.9 Pharmacological alteration of coactivation-induced perceptual and neural changes through application of memantine (N-methyl-D-aspartate [NMDA] receptor-blocker) and amphetamine. (A) Pharmacological modulation of coactivation effects on discrimination thresholds (mean ± SEM). The 3-h coactivation episode applied to the tip of the right index finger (IF) is indicated by *pink arrows* for the right hand and *gray arrows* for the left hand. For each group, discrimination thresholds obtained for the test finger (right IF) are shown pre- and post-coactivation and 24 h after coactivation (rec). For the control finger (left IF, which was not coactivated), thresholds are shown for the pre- and postcoactivation conditions. The general lack of effects for the control finger indicates the finger specificity of the coactivation protocol (in the placebo group) and a lack of unspecific side effects (in the drug groups). (B) Schematic projection of the average locations of the single equivalent N20-dipoles of the index finger pre- (*yellow symbols*) and postcoactivation (*red symbols*) onto a 3D reconstructed individual MRI dataset. Note the coactivation-induced shift toward the lateral and inferior aspects of the postcentral gyrus in the placebo group, which is nearly doubled in the amphetamine group but blocked under memantine. Comparable effects are lacking in the not-coactivated hemisphere (bottom row).

discrimination abilities was associated with small changes in cortical maps. On the other hand, those subjects who exhibited large cortical reorganization also had the lowest threshold (Pleger et al., 2003).

In recent years, intracortical excitability reflecting inhibitory and excitatory processes have been studied using paired-pulse stimulation techniques (Kujirai et al., 1993). The so-called paired pulse behavior is characterized by a significant suppression of the second response at short interstimulus intervals. To show that LTP- and LTD-like tactile protocols also affect cortical processing in a reciprocal way, SEP recordings after median nerve paired-pulse stimulation were performed before and after tHFS and tLFS. While tHFS increased excitability, tLFS reduced excitability. Similar to what had been described for BOLD signal changes, the amount of suppression was positively correlated with the individual gain in performance, indicating higher excitability in good learners (Höffken et al., 2007).

In addition to the analysis of local processing properties as described so far, a more complete understanding of the mechanisms mediating the effects of repetetive stimulation requires the investigation of global processes as provided by functional connectivity analysis. A study addressing connectivity on the basis of EEG signals recorded in sensorimotor cortical areas showed that after repetitive sensory stimulation, functional connectivity between somatosensory and motor areas was significantly enhanced (Freyer et al., 2012). Functional connectivity can similarly be well studied by means of analysis of the so-called resting state BOLD signals. After repetitive stimulation, strengthened intrinsic connectivity within the sensorimotor network in the postcentral gyrus contralateral to the stimulated hand was reported as wells as in associative brain regions, where intrinsic functional connectivity correlated positively with tactile performance and stimulation-induced improvement (Heba et al., 2017).

Event-related potentials allow analysis of cognitive process. A recent study by Reuter et al. (2014) was the first to demonstrate that repetitive stimulation affects not only early sensory processing, but also higher order cognitive processing. The authors reported that the amplitude of the latencies of the P300 component was reduced and amplitudes were increased (Reuter et al., 2014).

To investigate possible structural changes following repetitive sensory stimulation, we used high-resolution imaging together with voxel-based morphometry to study changes of gray matter (GM) volume. At baseline, tactile performance correlated with regional GM volume in the primary sensory cortex. After 45 min of repetitive stimulation, we observed an increase in GM volume in the left primary and secondary somatosensory cortices (Schmidt-Wilcke et al., 2017). These results show that structural changes in the brain, specifically in regions receiving afferent input from the stimulated body site, can be induced via a short-term intervention lasting only 45 min.

Combined, the available imaging and EEG data imply that repetitive sensory stimulation results in selective reorganization and remodeling of sensorimotor areas, where the amount of reorganization is related to the individual gain of perceptual abilities, with large reorganization found in good learners and *vice versa*. It is a common observation that the learning outcome varies substantially across individuals. The important insight from these studies is that individual learning differences were linked to individual differences in the amount of reorganization (see section 3.6 "Predicting Learning Outcome"). Furthermore, these data show that repetitive sensory stimulation does not affect isolated neural processing parameters. Instead, the entire means of neural processing, including structural and cognitive processing, appears remodeled, including the size and amount of activation, intracortical inhibition and excitation, functional connectivity, and gray matter volume. Conceivably, all these changes in concert might mediate the broad range of perceptual and behavioral alterations induced by repetitive stimulation (see section 3.8 "Generalization of training-independent learning outcome").

3.3 Pharmacological Mechanisms

Cellular studies suggest that there might be only a few fundamental mechanisms that control synaptic transmission. In particular, the N-methyl-D-aspartate (NMDA) receptor has been implicated in synaptic plasticity (Cotman et al., 1988). To demonstrate that repetitive sensory stimulation is mediated by basic plasticity mechanisms, its dependency on NMDA receptor activation was tested. To this aim, participants received a single dose of memantine, a substance known to selectively block NMDA receptors. In this placebo-controlled study, it was observed that memantine eliminated learning induced by repetitive sensory stimulation, both psychophysically and cortically (Fig. 21.10) providing strong evidence for the NMDA-receptor dependency of repetitive sensory stimulation-induced learning (Dinse et al., 2003a).

Another crucial player is GABA, which plays an important role in the maintenance of the balance of excitation and inhibition. GABA is therefore assumed to be critically involved in stabilizing ongoing processing as well as learning mechanisms. In humans, the role of GABA can be investigated through application of drugs that contain GABA agonists (lorazepam). After a single dose of lorazepam before repetitive sensory stimulation, the typically observed improvement of tactile acuity was completely blocked (Dinse et al., 2003b). These studies support the idea that repetitive sensory stimulation induces synaptic plasticity processes that are controlled by glutamatergic and GABAergic receptors.

While there are many approaches to block plastic processes pharmacologically, less is known about pharmacological agents that enhance cortical plasticity. *In vivo* experiments conducted in rodents, have shown that synaptic efficacy can be modulated by ligands of adrenergic and dopaminergic receptors, thereby gating synaptic plasticity and influencing learning (see reviews by Hansen and Manahan-Vaughan, 2014 and Hagena et al., 2016). Therefore single doses of amphetamine were used to test its modulatory role in learning processes evoked by repetitive sensory stimulation. Application of a single dose of amphetamine resulted in almost a doubling of both the normally observed improvement of tactile acuity and of cortical reorganization (Fig. 21.10) (Dinse et al., 2003a). Application of agonists or antagonists of the dopaminergic and cholinergic systems (Bliem et al., 2007, 2008) added further evidence that the processes underlying repetitive sensory stimulation are controlled and amplifiable through neuromodulatory systems. These data demonstrate that, using specific drugs, the outcome of coactivation can be further amplified, opening up the possibility for a systematic investigation of "neuroenhancement" of learning processes in human individuals.

3.4 Effects in a highly skilled Population—Musicians

The potential of repetitive stimulation is not limited to young adult subjects, but has been applied in musicians whose tactile performance is already enhanced. Therefore, the question was whether there is room for further improvement. Despite the better baseline performance, coactivation in musicians resulted in an even higher gain of tactile acuity. While the baseline performance correlated well with the duration of daily piano practicing, the coactivation-induced improvement also correlated with the number of years of extensive piano playing. These findings imply stronger capacities for

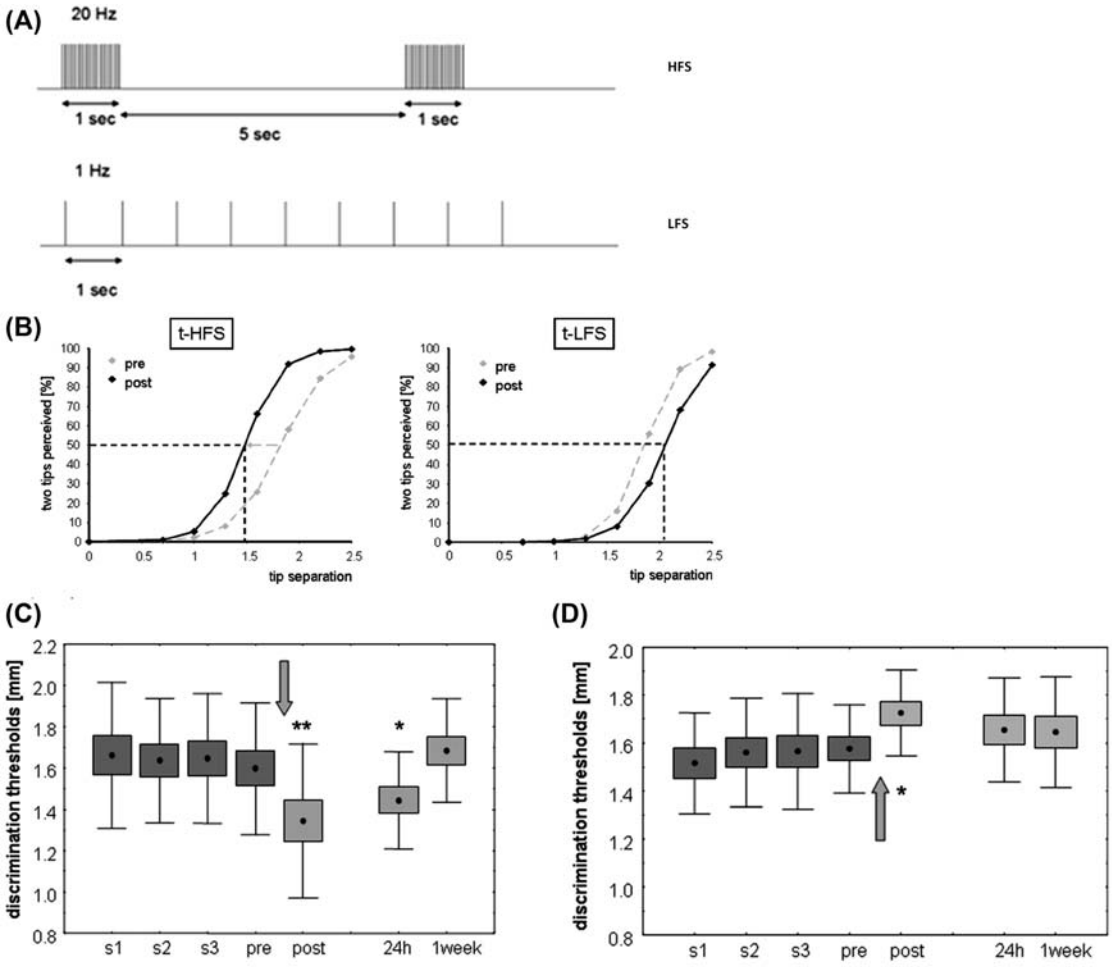

FIGURE 21.10 (A) Stimulation pattern used for high-frequency stimulation (HFS) and low-frequency (LFS) stimulation. (B) Psychometric functions (regression curves) illustrating the differential effect of 20 min HFS and LFS stimulation in two representative subjects. Correct responses in percent are plotted as a function of separation distance. 50% level of correct responses is indicated together with resulting thresholds (*dashed horizontal* and *vertical lines*). *Dashed gray lines* show precondition before and *solid black lines* postcondition immediately after HFS or LFS. After HFS there is a distinct shift in the psychometric functions toward lower separation distances. After LFS we found an analogous shift in the psychometric curve toward larger separations. Mean psychophysical effect of HFS (n = 14) (C) and LFS (n = 13) (D) on tactile discrimination thresholds of the right index finger. *Dots* represent mean thresholds, *boxes* show standard errors, and *whiskers* correspond to the standard deviation. Asteriscs show significant effects ($p<0.05$ and $p<0.001$). Time of HFS or LFS application was 20 min each (indicated by *arrow*). Shown are the results from four consecutive sessions before stimulation was applied. After HFS, discrimination thresholds were significantly reduced, which persisted up to 24 h after termination of HFS. One week after HFS, tactile discrimination thresholds recovered to baseline conditions. In contrast, after LFS, discrimination thresholds were significantly increased, indicating impaired tactile performance. 24 h after termination of LFS, discrimination thresholds recovered to baseline conditions. Reassessment of thresholds 1 week later revealed stable performance.

plastic reorganization in pianists, and point to enhanced learning abilities, which have been discussed in respect to metaplasticity (Ragert et al., 2004). Similar results have been reported for skilled craftspersons, characterized by better baseline performance (Reuter et al., 2014).

3.5 Role of Attention and Stress

Learning through training depends critically on attention and motivation. In case of repetitive sensory stimulation, which is believed to directly affect synaptic plasticity mechanisms because of the temporal protocols used, factors such as attention should play a minor role. The term "unattended activation-based learning" was coined to characterize the independence of passive learning from attentional processes (Dinse et al., 2005). However, the possibility remained that focused attention might have an influence through further enhancing plastic changes. We therefore took advantage of the short duration required to drive significant changes through passive stimulation to evaluate systematically the impact of attention on improvements in tactile performance induced by passive stimulation.

To test this hypothesis, three groups of subjects were subjected to the same repetitive sensory stimulation protocol. In group 1, subjects were asked to focus their attention on the stimuli of the repetitive sensory stimulation protocol. They were asked to note when the regular sequence of trains was interrupted by a missing train. In group 2, subjects had to perform an auditory oddball paradigm thereby drawing attention away from the stimulated finger and directing it toward a different sensory modality. In group 3, subjects had to perform a difficult mental calculation task to exhaust attentional resources. In all three groups, the learning outcome was similar. Moreover, we found comparable degrees of enhanced cortical excitability in all three groups tested. Our findings indicate that neither the amount of attention paid to the tactile stimuli, nor the degree of distraction, influenced the outcome of repetitive stimulation suggesting that focussed attention is not essential and/or beneficial for the efficacy of tHFS.

Cortisol, the primary glucocorticoid (GC) in humans, influences neuronal excitability and plasticity. Cellular studies demonstrated that elevated GC levels affect neuronal plasticity through a reduction of hippocampal long-term potentiation (Diamond et al., 2007). At a behavioral level, numerous studies reported impaired hippocampal functions after glucocorticoid treatment (Wolf, 2009). With respect to episodic memory, an impairing effect on memory retrieval has been repeatedly demonstrated (de Quervain et al., 2000). To investigate a possible role of stress on the effects of repetitive sensory stimulation, we explored the impact of elevated cortisol levels on human perceptual learning. Our results showed that a single administration of hydrocortisone (30 mg) completely blocked changes induced by repetitive sensory stimulation in tactile acuity. In contrast, the placebo group showed the expected increase in two-point discrimination of over 14%. These data demonstrate that elevated glucocorticoid levels block human tactile perceptual learning, presumably caused by suppressed long-term potentiation. Moreover, these data indicate that the effects of glucocorticoids go beyond the limbic system (Dinse et al., 2016).

3.6 Predicting Learning Outcome

It is an everyday phenomenon that there are good and bad learners, which also holds true for perceptual learning under laboratory conditions (Fahle and Henke-Fahle, 1996). Why this is the case remains mostly elusive. There are many factors that can lead to poor learning: for example, impairments at the level of the sensory periphery that prevent inputs from getting into brain areas that learn. A lack of attention, or an impairment of learning mechanisms as is the case in BDNF polymorphism (Kleim et al., 2006), can also be confounding factors.

Repetitive sensory stimulation is particularly suited for the study of learning variability, because attention can be excluded as a potential contributing factor. One EEG study used repetitive sensory stimulation to demonstrate that spontaneous EEG rhythms recorded in somatosensory cortex (μ-rhythm) are another important predictor for learning. Because the somatosensory μ-rhythm is in the 10 Hz range, it is also referred to as α-rhythm. It was observed that two independent processes explained about 65% of the learning variance: High learning, as assessed by high gains in tactile acuity, was observed when a participant showed high spontaneous α-power before repetitive sensory stimulation. In addition, high learning occurred when a high event-related desynchronization occurred during repetitive sensory stimulation. These data imply that brain states are another important factor that influences learning (Freyer et al., 2013). This offers the exciting practical option to manipulate baseline α-power through neurofeedback to control the learning outcome.

In section 3.3 (Pharmacological Mechanisms), a crucial role in controlling stimulation-induced plasticity and learning was described for GABA. In another study using magnetic spectroscopy imaging, the role of baseline GABA was investigated. This study showed that about 54% of the variance of the learning outcome following an LTP-like protocol could be explained by the individual level of GABA measured in a voxel centered about the individually assessed hand representation (Heba et al., 2016).

3.7 Studying Hand–Face Learning Transfer—A Unique Advantage Offered by Repetitive Sensory Stimulation Approaches

Tactile inputs arising from neighboring skin portions are processed in the brain in neighboring regions as well. The resulting body representation in somatosensory cortex is referred to as a homunculus. One prominent exception from this neighbor-preserving mapping is the face–hand border, where fingers and face are located side by side, although they are physically apart. Reduction of tactile inputs following amputation, or deafferentation, induces perceptual changes across this border that are explained by plastic competitive mechanisms striving for cortical territory (Ramachandran et al., 1992). To explore possible cross-border learning transfer, the right index finger was stimulated using a standard repetitive sensory stimulation protocol. This improved tactile perception, not only at the right stimulated index finger, but also at the unstimulated right cheek and upper lips. These findings demonstrate that learning-induced perceptual improvement can cross the face–hand border, suggesting that mechanisms other than competition, such as facilitation-based

plasticity, might operate during learning-induced reorganization (Muret et al., 2014). Further experiments are needed to clarify whether these transfer properties can be used as intervention to treat impairments in the face regions through stimulation of the fingers.

3.8 Generalization of Training-Independent Learning Outcome

Training a specific task improves performance in this task. However, improvements are specific for the trained task, with little transfer to other tasks. Against the background of potential application as intervention, much research is currently devoted to overcome this "curse of specificity" so that training outcome more readily transfers in a broad range, preferentially to real-life situations.

A central aspect of repetitive sensory stimulation is that improvement of perception is not induced through task training, but through modification of synaptic transmission in neural networks. In this sense, repetitive sensory stimulation is task-independent. This view predicts that repetitive sensory stimulation not only affects acuity thresholds, but also affects the entire means of neural processing related to tactile, haptic, and sensorimotor information processing. Therefore, in a series of experiments, other tactile, haptic, and sensorimotor abilities were tested. In fact, after repetitive sensory stimulation better performance was observed for tactile acuity (as measured by two-point or grating discrimination), frequency discrimination, dot-pattern discrimination, haptic object recognition, tactile reaction times, and decision-making, as well as sensorimotor performance such as dexterity (Dinse et al., 2005, 2011). This broad range generalization of positive effects is an important prerequisite to use repetitive sensory stimulation protocols as therapy and intervention in patients (see Section 3.11).

3.9 Repetitive Sensory Stimulation in Other Sensory Modalities

If it is true that the temporal properties of the repetitive sensory stimulation protocols induce synaptic plasticity directly, this should then be true for all sensory modalities. For the nociceptive system, bidirectional changes of pain perception had been reported following modified LTP- and LTD-like stimulation of human subjects (Klein et al., 2004). A number of studies in the visual system showed that repetitive sensory stimulation using LTP-like and LTD-like presentations of visual stimuli analogue to those used in the tactile system induced comparable changes of visual perception (Teyler et al., 2005; Clapp et al., 2012). In another study, patterned stimulation of the dorsolateral geniculate nucleus induced synaptic plasticity in the adult visual cortex of behaving rats (Tsanov and Manahan-Vaughan, 2007). A functional magnetic resonance imaging (fMRI) study using the same paradigm demonstrated a bilateral increase in BOLD signal after stimulation that was confined to extrastriate areas when the stimulated hemifield was presented with the checkerboard stimulus (Clapp et al., 2005).

Using LTP-like stimulation with oriented gratings, improvement of orientation discrimination performance could be induced after 40 min of stimulation with oriented bars or gratings (Marzoll et al., 2018). Testing the specificity of induced changes showed that the resulting improvement showed little signs of feature specificity as typically observed after training-based perceptual learning. These findings could point toward a fundamental difference between stimulation- and training-induced learning processes. Administering a face identity change detection task before and after a passive LTD-like stimulation protocol revealed plastic changes of face detection, suggesting that this approach is also possible using more complex visual stimuli (Pegado et al., 2016).

Recent data have provided evidence that repetitive sensory stimulation is also effective for the auditory domain. Using an intermittent, high-frequency protocol consisting of auditory stimuli was effective in driving cross-modal plasticity in patients with hemianopia (Lewald et al., 2012). In an earlier report (Clapp et al., 2012), high-frequency, repetitive, auditory stimulation induced a long-lasting increase of the human auditory evoked potential (AEP). In other studies, passive listening of sounds has been shown to improve their discriminability (Amitay et al., 2006), and learning was further enhanced by combining an auditory frequency-discrimination task with additional exposure to acoustic stimuli that roughly matched the sounds from the material used for practicing (Wright et al., 2010). Together these data indicate that repetitive sensory stimulation is in fact effective beyond the somatosensory system. However, further experiments are needed to clarify possible modality-specific properties that may constrain the amount and the kind of plasticity.

3.10 Efficacy of Repetitive Sensory Stimulation in Elderly Individuals

Aging instigates major reorganization and remodeling at all levels of brain structure and function, which is paralleled by a progressive decline of mental and physical abilities (Hof and Mobbs, 2001). On the other hand, it is now well documented that age-related changes are not a simple reflection of degenerative

processes but rather a complex mix of plastic, adaptive, and compensatory mechanisms, suggesting that brain plasticity is operational into old age (Dinse, 2006). Considering the current demographic changes in many civilizations, there is an urgent need for measures permitting an independent lifestyle into old age. Therefore, strategies such as training, exercising, practicing, and stimulation that make use of neuroplasticity principles are essential to maintain health and functional independence throughout a lifespan.

Sensory processes gradually lose their efficiency in old age. Glasses and hearing aids are a standard aid for elderly people. However, in contrast to vision and hearing, the dramatic age-related deterioration of the sense of touch goes mostly unnoticed because there are no conditions such as reading newspapers or obtaining a driver's license, which might reveal this impairment. As a result, the sense of touch and its vital role for coping with activities of daily living are widely underestimated. Elderly individuals progressively adapt to the loss of high-level tactile performance and learn to compensate by developing behavioral strategies, such as relying more on visual control to overcome the decrement in the sense of touch.

At a perceptual level, there is agreement that tactile acuity is significantly reduced during aging. Interestingly, tactile acuity declines much more vigorously for some body regions than for others. According to one study (Stevens and Choo, 1996), deterioration of acuity in the great toe averaged about 400% between young and elderly subjects (aged 65–87 years) as compared with an average decline of 130% observed on the fingertip.

To test the efficacy of repetitive sensory stimulation in elderly, a group of 66–86-year-old healthy individuals were stimulated using a repetitive sensory stimulation protocol and the results were compared with a group of young adults and middle-aged adults of 47–55 years of age. Before stimulation, the discrimination thresholds of individuals under 60 years of age were better than those aged 60 years and older. After stimulation, this difference disappeared and the tactile acuity of the older individuals matched the average performance of participants aged 45–60 years (Fig. 21.11). Interestingly, participants who had the highest thresholds at baseline (prestimulation) showed the largest improvement, while participants with low thresholds (better acuity) had only limited improvement. This finding suggests that elderly individuals with the largest tactile impairment benefited most from the treatment (Dinse et al., 2006).

Repetitive stimulation in elderly individuals was also shown to restore haptic and sensorimotor performance to a considerable extent. Of particular interest were findings that repeated application of repetitive stimulation over several weeks resulted in a stabilization of tactile improvement for 2 weeks or more, providing a way to

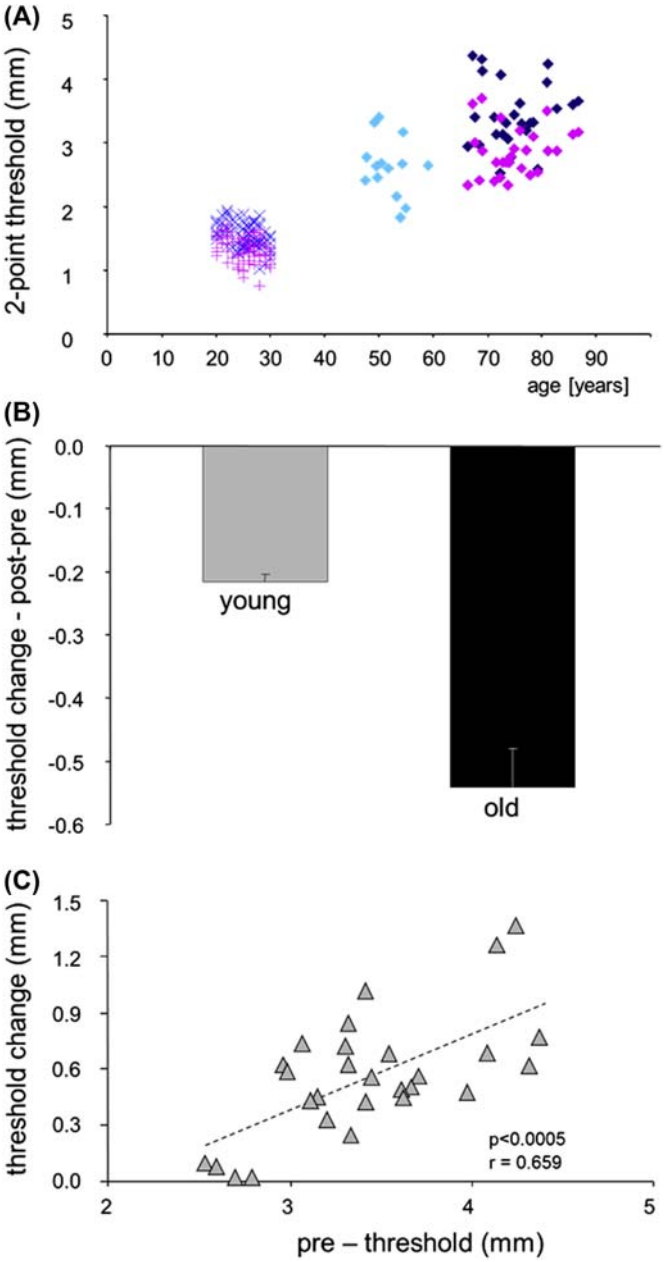

FIGURE 21.11 Effects of repetitive stimulation protocol (coactivation) on age-related degradation of tactile acuity of elderly participants. (A) Tactile two-point discrimination thresholds of the tip of the right index finger as a function of age (total of 120 subjects). After coactivation (*violet symbols*), thresholds of the coactivated subjects (young control group and elderly group) were significantly reduced. Coactivation-induced improvement in the group aged 66–86 years was several-fold stronger in magnitude compared with the young subject. As a result, after coactivation thresholds of the elderly resembled those found in the subjects aged 47–55 years. (B) Comparison of the amount of coactivation-induced lowering of discrimination thresholds between young and elderly. Shown are average pre–post differences in threshold and standard error. (C) Linear correlation analysis (Pearson's) between thresholds on the right index finger under preconditions and the magnitude of discrimination threshold changes (post–pre). The significant correlation indicates that pre-thresholds determine the amount of coactivation-induced improvement, and thus participants with the worst baseline performance profited most from the coactivation approach.

make the beneficial effects of passive stimulation more long-lasting (Kalisch et al., 2010).

To clarify the nature of neural changes and the mechanisms underlying remodeling of age-related decline, we combined fMRI with assessments of tactile acuity, perceptual learning, and computational modeling. First, we could show that aging leads to tactile degradation parallel to enhanced activity in the somatosensory cortex. Using repetitive sensory stimulation, we were then able to partially restore tactile acuity, which, however, was not accompanied by the expected attenuation of cortical activity, but was rather accompanied by a further enhancement as observed in young adults. Accordingly, we observed two different types of increased cortical activation: One type was associated with age, but was also linked to impaired perception, and the other type was associated with learning and linked to perceptual improvement (Pleger et al., 2016). Computational modeling solved this apparent discrepancy by showing that different aspects of inhibition are responsible for the age-related decline of tactile acuity on the one hand, and of the learning-induced improvement, on the other hand. While lateral inhibition is affected by aging, learning targets the amplitude of inhibition (Pleger et al., 2016). Taken together, these studies demonstrate that despite the accumulation of degenerative processes, the typical age-related decline of perception is not irreversible but can be ameliorated through repetitive sensory stimulation protocols.

3.11 Application of Repetitive Sensory Stimulation—Use in Brain Injury Rehabilitation and Pain Treatment

Sensorimotor impairments resulting from brain injury and stroke can have extensive physical, psychological, financial, and social implications, despite the available neurorehabilitative treatments. In particular, the loss of sensory abilities further complicates the individual's ability to use the hand for real-life situations in spite of possible recovery of motor functions. Neuroplasticity-based rehabilitation after brain injury and stroke uses task-specific training and massed practice to enforce brain plasticity to improve sensorimotor functions (Taub et al., 2002), but still a significant percentage of patients suffer from long-term invalidity (Kwakkel et al., 2004). Therefore, the development of additional approaches that may supplement, enhance, or even replace conventional training and rehabilitation procedures is essential to also make treatment feasible over longer periods of time, taking into account both costs and compliance.

So far, the feasibility and effectiveness of repetitive sensory stimulation as a therapeutic intervention has been investigated in cooperation with rehabilitation centers in subacute and chronic stroke patients with the goal of improving tactile, haptic, and sensorimotor functions of the upper extremities. The rational was to enforce plastic processes within and around those brain areas that became dysfunctional, to facilitate recovery and compensation (Dinse et al., 2011). For stimulation, LTP-like protocols of electrical pulses were delivered to all fingers of the affected hand. Recent studies used a stimulation glove with in-built contacts on each fingertip.

In a randomized, sham-controlled clinical study, a group of subacute patients (aged 34–89 years) were studied to compare the effects of a combined therapy (repetitive sensory stimulation plus standard therapy including specific hand/arm training) with standard therapy and specific hand/arm training alone (treatment 2 weeks, 40 min per day, 5 days per week). Hand/arm training consisted of ergotherapy and activities of daily living training. Compared with standard treatment, the combined therapy was superior in the domains of sensory, motor, and proprioceptive functions as well as in everyday tasks (Kattenstroth et al., 2018). To analyze how the positive effects were distributed across the more severe or less severe patients, we subdivided the data according to the median of the total performance. This analysis revealed that the pre–post improvement for the more severe patient subgroup was much higher than for the less severe subgroup. Furthermore, this study showed that patients tolerated the repetitive sensory stimulation treatment well, as well as the application using a custom-made stimulation glove (Kattenstroth et al., 2018).

In another study on chronic stroke patients (average post stroke time 30 months), individuals were treated with repetitive stimulation for 4 days a week for 4 weeks on all fingers of the affected hand but without any additional hand–arm therapy. Retesting after 4 weeks revealed significant improvements of sensory and motor performance of the affected hand. Remarkably, after a follow-up of 6 weeks, the same magnitude of improved sensorimotor performance could be observed indicating long-lasting benefits (Smith et al., 2009).

The particular advantage of repetitive sensory stimulation is its passive nature, which does not require the active participation or attention of subjects. As a consequence, repetitive sensory stimulation approaches can be applied in parallel with other techniques or other occupations, which makes this intervention very easy to implement and more acceptable to the individual. Therefore a series of single case studies were initiated, where patients were treated with repetitive sensory stimulation protocols, in which the stroke dated back more than 10 years (Kattenstroth et al., 2012). In all cases, repetitive stimulation was applied at the homes on a regular basis (5 days a week, for 45–60 min per day). In all cases,

beneficial effects on tactile and sensorimotor behavior were observed, which, however, developed in some cases only after months of stimulation and continued to increase on a timescale of months (Fig. 21.12).

The available data show that the positive effects of repetitive sensory stimulation in subacute patients can be quite long-lasting when applied on a regular schedule over weeks. Furthermore, positive effects in long-term chronic patients might emerge only after months of intervention. For these reasons, it appears conceivable that the concept of repetitive sensory stimulation is highly suited for interventional approaches, either in combination with other rehabilitation measures or as stand-alone approach. A particular advantage, besides low costs, is the high compliance due to using it by patients at their homes over extended periods of time, an aspect most crucial for chronic patients.

Complex regional pain syndrome (CRPS) is a chronic pain syndrome, which is characterized by sensory, autonomic, and motor disturbances. Aside from pharmacological treatment, rehabilitation based on concepts to induce neuroplasticity, such as sensory training, mirror therapy, or graded motor learning, is currently used to improve the sensorimotor limb function and to reduce pain. A first treatment study applying repetitive stimulation on five consecutive days demonstrated a high feasibility and efficacy of LTP-like stimulation in CRPS patients to improve sensory loss, therefore providing an essential prerequisite for rehabilitation of hand function. Qualitatively, stimulation effects were similar to those observed in healthy controls, indicating intact cortical processing of tactile stimuli in patients with CRPS type I. In addition, current pain intensity decreased in 4 out of 16 patients by $\geq 30\%$. While the limited impact on pain relief might be due to the short stimulation period, the overall beneficial effects suggest the usage of repetitive stimulation also in the treatment of chronic pain; however, more studies are needed (David et al., 2015).

3.12 Time Course and Stability of Effects of Repetitive Sensory Stimulation

Little is known about the stability and maintenance of tactile performance in healthy individuals under everyday life conditions. Data from human subjects whose arms and fingers were immobilized, because they had to wear a cast, revealed that tactile acuity dropped significantly within 1–2 weeks of immobilization (Lissek et al., 2009). These findings indicate that performance is not stable without maintained practice and use.

When passive stimulation was applied in a single session, beneficial effects persisted up to 24 h or more, depending on the protocol used (for a detailed discussion of stability of effects see Dinse et al., 2005; Kalisch et al., 2010). A crucial prerequisite for using passive stimulation as a tool in intervention is long-term persistence of induced perceptual and behavioral improvements. Applying repeated application of repetitive stimulation in elderly individuals on a biweekly basis for 4 weeks resulted in prolonged effects where tactile acuity recovered to baseline only within 2 weeks, while the gains in haptic and motor performance were preserved at least for 2 weeks (Kalisch et al., 2010). When, in stroke patients, repetitive stimulation was applied

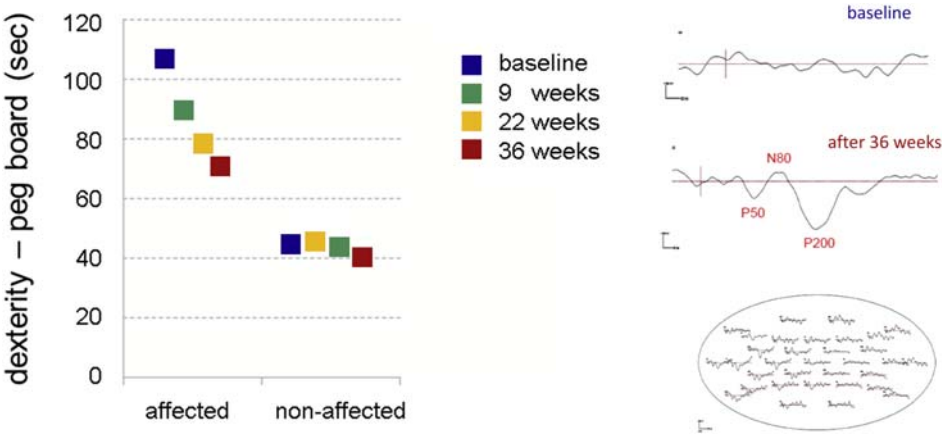

FIGURE 21.12 Beneficial long-term effects of repetitive sensory stimulation treatment in a chronic patient with brain injury (intracerebral hemorrhage secondary to thalamic vascular malformation). Injury dated back 11 years when treatment with repetitive sensory stimulation was initiated, which lasted 36 weeks. Left: Pegboard (dexterity) test performance for the affected and nonaffected hand at different time points. Note substantial improvement over the entire time course of stimulation. Right: Somatosensory evoked potentials (SEPs) obtained from high-density EEG recording at electrode C3 during tactile stimulation of the little finger (d5) of the affected hand. *Vertical red line* represents stimulus onset. While before intervention no SEP was detectable (*blue*), a clear P50, N80, and P200 indicative of normalized tactile somatosensory cortex processing could be obtained after 22 weeks of intervention (*red*).

for several weeks on a daily basis, follow-up measurements revealed full maintenance of beneficial effects up to 3 months following termination of stimulation. Thus, long-term, repeated application of passive stimulation is highly effective to drive sustained alterations.

3.13 Magnitude of Effects of Repetitive Sensory Stimulation

As a rule, acuity improvement after passive stimulation is in the range of 10%–20%. Given these numbers, it is not *a priori* clear whether such an improvement represents a major advance that is relevant for everyday life. In other words, to what extent are training-based improvements of sensory skills comparable in magnitude to those evoked by short periods of passive stimulation? We therefore compared acuity changes induced by various protocols of passive stimulation applied for minutes to hours with acuity changes found in musicians or in blind individuals as a result of a yearlong training. Surprisingly, acuity changes for pianists, violinists, or blind individuals are almost identical to those obtained after short-periods of passive stimulation (Dinse et al., 2005).

3.14 Earlier Evidence Against Passive Learning

There is agreement that attention plays an essential role in perceptual learning and experience-related plasticity. Following this view, many studies have shown that learning appears to depend on whether subjects focus their attention to specific features. Research of this type has been taken as support for the hypothesis that subjects need to be aware of and focus their attention on a stimulus feature for that feature to be learned. In fact, close inspection of the literature reveals that much of the apparent evidence showing a role of attention in perceptual learning was presented as evidence against passive learning (Seitz and Dinse, 2007). Of particular interest were experiments that provided evidence that perceptual learning does not necessarily depend on selective attention. Subjects were repeatedly presented with a background motion signal so weak that its direction was not visible and that was irrelevant to the central task. However, the repetitive exposure improved performance specifically for the direction of the exposed motion, when tested in a subsequent suprathreshold test (Watanabe et al., 2001).

On the other hand, others reported that prolonged and "passive" stimulation is not sufficient to drive plastic changes. In studies of auditory learning, pairing of sensory stimulation with electrical stimulation of the *nucleus basalis* result in rapid and selective reorganization of cortical maps (Kilgard and Merzenich, 1998). However, control experiments revealed that sensory stimulation alone without stimulation of the *nucleus basalis* was ineffective. Similarly, passive exposure to tactile stimulation in monkeys, who had to perform an auditory discrimination task, had no effect on tactile discrimination abilities (Recanzone et al., 1992a,b). These apparent discrepancies with our data derived from passive stimulation can be settled in the light of the experiments using single-site stimulation only (Pleger et al., 2003; Ragert et al., 2008). Under these conditions (i.e., small field or single-site stimulation), no effects were observed, neither on discrimination abilities nor on cortical processing. Accordingly, to be effective, sensory stimulation must incorporate principles such as spatial (coactivation) and/or temporal (high-frequency) summation.

3.14.1 *High Efficiency of Repetitive Sensory Stimulation due to Canonical Plasticity Protocols*

The described efficiency of repetitive sensory stimulation protocols might come as a surprise. A fundamental assumption is that repetitive stimulation directly drives synaptic plasticity processes in the cortical areas representing the stimulated sites. To explain this effectiveness, a conceptual framework was suggested, where sensory learning occurs when sensory inputs pass a learning threshold (Fig. 21.13). Under normal conditions, sensory inputs are too weak to pass the learning

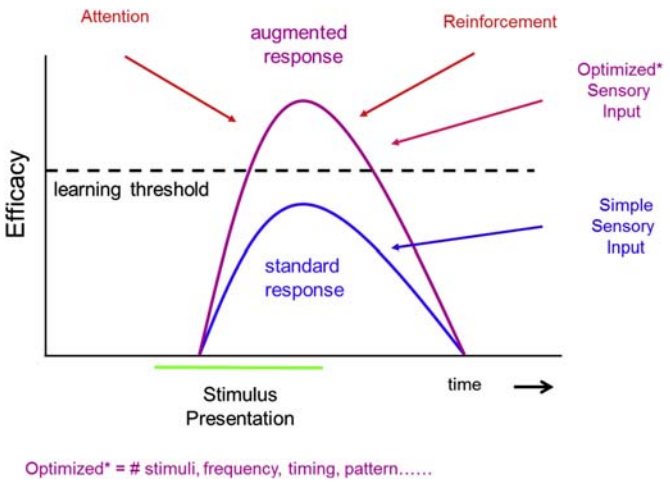

FIGURE 21.13 Conceptual framework depicting factors that control learning. For sensory stimulation to be sufficient, it must drive the neural system past the point of a learning threshold. Responses evoked by simple sensory stimulation fail to induce learning. Factors such as attention or reinforcement play a critical permissive role in training and practice-based learning conditions. On the other hand, all factors that relate to the timing and temporal structure of stimulation such as high-frequency or burstlike pattern alternatively optimize simple inputs by driving them across the learning threshold without requiring attention or motivation.

threshold. Factors that play an important role in training-based learning are attention, reward, and motivation, thereby amplifying the sensory inputs that are otherwise below threshold. In case of repetitive sensory stimulation, factors such as attention either play no role or make only a small contribution. Instead, factors that "optimize" sensory inputs in case of repetitive stimulation are high-frequency or burstlike features as well as heavy schedules of stimulation (i.e., large number of sensory stimuli), which boost inputs that are normally insufficient to drive learning past this learning threshold.

The validity of repetitive sensory stimulation across sensory modalities supports the idea that the temporal structures and pattern used are ubiquitous. It is therefore conceivable that there are only a few, canonical, conditions that effectively drive plasticity. If this is true, this will readily explain the remarkable efficacy of the repetitive stimulation. An open question is whether the observed dichotomy into low- and high-frequency stimulation is due to ecologic constraints where these frequencies prevailed. Alternatively, molecular and biochemical properties might have constrained the development of these temporal pattern.

3.14.2 *Are Repetitive Sensory Stimulation Evoked Changes a Form of "Learning?"*

Throughout this chapter repetitive sensory stimulation effects were denoted as "learning." The rationales for this were based on empirical data according to which the effects of repetitive stimulation (1) depend on NMDA-receptor activation, thus demonstrating that the effects are mediated by basic mechanisms underlying synaptic plasticity, and (2) induce facilitation of intracortical excitability. Both observations characterize fundamental principles underlying "learning."

In a more general view, learning is defined as the acquisition of new knowledge, behaviors, skills, values, preferences, or understanding and may involve synthesizing different types of information. Human learning may occur as part of education, personal development, or training. It may be goal oriented and may be aided by motivation. Apparently, the term "learning" is rather broadly defined and is not restricted to the everyday life concept of acquiring knowledge as is the case during school learning or learning a task after training. Given such a broad definition, the outcome following repetitive sensory stimulation qualifies readily as learning, as captured in the term "training independent sensory learning."

4. CONCLUSIONS

The data presented here provide strong evidence that pure exposure to sensory stimulation alters perception, behavior, and cognition in a stimulation-dependent way. However, to be efficient, stimulation must conform to requirements described for protocols aimed at specifically altering synaptic transmission and synaptic efficacy. Thus, the available data show that the application of canonical protocols fundamental to regulating and controlling synaptic plasticity can be used directly to interfere with human behavior. From that it is concluded that the usage of canonical stimulation protocols might be an ultimate way to induce learning processes. The persistency of changes, the ease of application, and the wide range of effects make passive stimulation an ideal tool in the targeted intervention for improving perception, behavior, and cognition.

5. PERSPECTIVES AND OUTLOOK

- Stimulation protocols: Although the current available protocols show a remarkable efficiency, there is still a need for making them even more efficient in terms of duration needed and magnitude and stability of effects.
- Reorganization beyond early stages: In terms of assessment of cortical changes, most studies so far focused on early stages of sensory processing. More studies are needed to find out and to understand changes in higher areas. Similarly, so far little is known about subcortical changes induced by repetitive sensory stimulation.
- Memory processes: Up to now consolidation processes have not been addressed, for example, the role of sleep for stabilizing stimulation-induced effects remains elusive.
- Neuroenhancement: Besides drug-enforced neuroenhancement, many attempts are currently under way to push learning processes, among many of them unexpected such as action video game playing, arts, dance, neurofeedback, and imagination. A lot of research needs to be done to evaluate their role in pushing stimulation-induced plastic changes.
- Rehabilitation: The treatment of upper limb sensorimotor impairment in stroke patients or patients suffering from brain injuries should be extended to lower extremity impairment, requiring development of adequate stimulation devices. Besides, there is a need for extending the spectrum of pathological conditions where repetitive sensory stimulation can be used.
- Targeting cognition: In principle, induction of plastic changes through repetitive stimulation should not be limited to sensorimotor domains but should be similarly effective to affect also higher order cognitive functions. Promising data come from central

stimulation approaches that demonstrated enhancement of cognitive performances.
- Product development: On the long run, stimulation devices must be developed that can be used under rigorous everyday conditions by non-expert individuals in their homes.
- Conceivably, given that repetitive sensory stimulation is a rather new development, we are only at the beginning of an era, where targeted brain manipulation will offer completely new scenarios of learning, with implications that can be hardly foreseen.

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Volume 28

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